Chemoselective Polymerizations from Mixtures of Epoxide, Lactone, Anhydride, and Carbon Dioxide


Published in:
Journal of the American Chemical Society

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Publisher rights
Copyright 2016 the authors.
This is an open access article published under a Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution and reproduction in any medium, provided the author and source are cited.

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.
Chemoselective Polymerizations from Mixtures of Epoxide, Lactone, Anhydride, and Carbon Dioxide

Charles Romain,*‡ Yunqing Zhu,† Paul Dingwall,† Shyeni Paul,† Henry S. Rzepa,‡ Antoine Buchard,‡ and Charlotte K. Williams*‡

‡Department of Chemistry, Imperial College London, London SW7 2AZ, U.K.
‡Department of Chemistry, University of Bath, Bath BA2 7AY, U.K.

ABSTRACT: Controlling polymer composition starting from mixtures of monomers is an important, but rarely achieved, target. Here a single switchable catalyst for both ring-opening polymerization (ROP) of lactones and ring-opening copolymerization (ROCOP) of epoxides, anhydrides, and CO₂ is investigated, using both experimental and theoretical methods. Different combinations of four model monomers—ε-caprolactone, cyclohexene oxide, phthalic anhydride, and carbon dioxide—are investigated using a single dizinc catalyst. The catalyst switches between the distinct polymerization cycles and shows high monomer selectivity, resulting in block sequence control and predictable compositions (esters and carbonates) in the polymer chain. The understanding gained of the orthogonal reactivity of monomers, specifically controlled by the nature of the metal-chain end group, opens the way to engineer polymer block sequences.

INTRODUCTION

Discovering selective transformations using monomer mixtures to yield polymers of homogeneous compositions, including block sequences, are highly desirable both to reduce costs and to enhance chemical complexity.¹ Block copolymers are important in commodity applications but also allow finer control of properties thereby allowing tailoring for higher-value applications.² Pioneering monomer sequence selectivity has been demonstrated in processes including controlled radical polymerizations, stepwise monomer coupling reactions, and ring-opening metathesis polymerization.³−⁵ Nonetheless, significant challenges remain, particularly to expand the methods to oxygenated polymers and to allow controllable enchainment from mixtures. Methods to switch polymerization reactions “on/off” or between different catalytic cycles are generally useful and will be essential to enable block selectivity and diversity.⁶ Matyjaszewski and co-workers pioneered an electrochemical “switch”, controlling the oxidation state and reactivity of Cu catalysts for atom transfer radical polymerizations.⁷ Furthermore, photoelectrochemical triggers can be used to control radical polymerizations.⁸ In the distinct area of lactone ring-opening polymerizations (ROP), it is also feasible to switch on/off the reactivity of metal alkoxide catalysts by changing the oxidation state.⁷ Using this method it was even possible to discriminate between two very similar monomers, lactide and ε-caprolactone, in ROP.⁹ Mirkin and co-workers demonstrated allosteric switchable polymerization catalysts, whereby the addition of halide ions switched the catalyst conformation enabling a switch on/off ROP.⁸ Dubois, Coulombier, and co-workers developed a switch process for ROP of lactone and cyclic carbonates that is controlled by the presence/absence of carbon dioxide.⁹

Kinetic control is of long-standing interest as a means to control polymer composition from mixtures, albeit requiring that a common polymerization method is used. For example, Coates and co-workers discovered that the ring-opening copolymerizations (ROCOP) of an epoxide, anhydride, and carbon dioxide occurred with very high selectivity to yield only block copoly(ester-carbonates).¹⁰ The ROCOP of epoxide/anhydride occurred first, followed by epoxide/CO₂ polymerizations. Subsequently, various other ROCOP catalysts showed the same selectivity allowing various new semi-aromatic polyesters to be prepared.¹¹,¹² Albertsson and co-workers exploited differences in polymerization rates, enhanced using thermal switches, in the ROP of ε-caprolactone and a cyclic carbonate to prepare multi-block copolymers.¹³ Stereochemical control is a special case of kinetic selectivity, an outstanding control in lactone ROP was first demonstrated by Coates and Thomas using chiral catalysts and racemic mixtures of two similar, but subtly different, lactones to yield syndiotactic polyesters.¹⁴

Another strategy in block selectivity is to link together two different polymerization cycles, in the best cases these occur via “one-pot” processes using tandem catalysis and sequential monomer additions.¹⁵ For example, Darenbourg and Lu...
applied organocatalysts for lactide ROP which were subsequently deactivated by water addition, allowing a second metal catalyst to initiate the ROCOP of epoxide/CO₂. Hadjichristidis and Gnanou prepared block copoly(ether-ester/carbonates) using base-catalyzed epoxide ROP, followed by addition of an organo-catalyst to deactivate the base and simultaneously initiate lactone/cyclic carbonate ROP.

In 2014, our group reported the first example of a single catalyst, I (Supporting Information (SI), Figure S1), which was active for two distinct polymerization cycles and which could be “switched” between them by a new type of chemoselective control. The selectivity arises by controlling the chemistry of the metal–polymer chain end group, with metal alkoxides and carbonates having orthogonal reactivities toward the monomers. Using this method, mixtures of cyclohexene oxide, ε-caprolactone, and carbon dioxide were first polymerized by ROCOP (epoxide/CO₂) to produce a perfectly alternating polycarbonate block and, once the carbon dioxide was consumed/removed, the same catalyst selectively polymerized the lactone, by ROP, ultimately producing block copoly(ester-carbonates). This surprising result was rationalized by kinetic phenomena: i.e., relatively faster rate of carbon dioxide insertion into the zinc alkoxide intermediate, which is common to both catalytic cycles. To our knowledge such chemoselective control is conceptually and practically distinct from the previous switches because it operates via control of the chemistry of the chain end group and it applies just one catalyst (and pot) for two distinct polymerization cycles (Scheme 1). Exploiting the “chemoselective switch” allows epoxides to be used to switch-on catalysts, such as I, for efficient ROP of lactones. Furthermore, it can be used to selectively prepare ABA type block copoly(ester-carbonates). Very recently, it was used to prepare multi-block copolymers, using mixtures of ε-decalactone, phthalic anhydride, and epoxides and switching between ROCOP (epoxide/anhydride) and ROP (lactone). Despite the promising results, the fundamental basis for the selectivity is not yet understood. Here, we combine experimental and theoretical studies to examine the thermodynamic factors under-pinning the selective transformations.

**RESULTS AND DISCUSSION**

A detailed study comparing the products of polymerizations conducted using mixtures selected from four generic types of oxygenated precursors was undertaken (Scheme 2). The

---

**Scheme 1. Three Distinct Polymerization Catalytic Cycles Which Are Feasible from the Zinc Alkoxide Intermediate**

**Scheme 2. Four Exemplar Monomers and the Range of Polymer Products Produced Using Chemoselective Catalysis**

---

**Figure 1.** Poly(carbonate-block-ester) formation from mixtures of ε-caprolactone (ε-CL), cyclohexene oxide (CHO), and CO₂.
trations of monomer from 1 to 8 M (Table S1). However, the rapid and quantitative ROP of ε-CL was possible after the addition of epoxide, either as a sub-stoichiometric quantity (≈10 equiv vs 1, in toluene) or as the solvent (Figure 1 and Table 1, runs 1–4). The “switch-on” of ROP occurred due to the reaction of 1 with the epoxide to form an alkoxide intermediate, which was characterized by in situ using FTIR spectroscopy (Figure S1). The spectrosopic study confirmed that the acetate co-ligand of catalyst 1 attacks CHO, forming a zinc alkoxide; it is this alkoxide which is an active initiator for ROP (Figure 2).

The rapid polymerization of ε-CL, catalyzed by 1 in the presence of epoxide, over a range of loadings (1:monomer 1:200–800 mol/mol), results in quantitative conversion to poly(caprolactone) (PCL) in less than 1 h (Table 1, runs 1–4). The PCL molecular weight (MW) can be controlled over the range 6–45 kg mol⁻¹ (Table 1 and Figure S2). The catalyst system is highly active, having a turnover frequency of 620 h⁻¹ (Table 1, run 4), which compares well with some of the best systems. The polymerization control is high, as assessed by an aliquot method; there is a linear relationship between MW and time (Figure 3) and a linear relationship between MW and a linear relationship between MW and the catalyst concentration (Figure 3). Importantly, despite there being two strained heterocycles present, both of which could undergo ROP, there is no evidence of incorporation of any epoxide either in the polyester, i.e., no ether linkages, or as a separate polyether. That is, the catalyst is highly selective for lactone ROP.

When catalyst 1 is reacted with a mixture of ε-CL, epoxide, and CO₂, only polycarbonate (PCHC) is formed (Table 1, run 5), and under these conditions there is no lactone incorporation (see Figure S3). Further, polymerizations using mixtures of lactone, epoxide, and CO₂ conducted using high concentrations of ε-CL (Table 1, entries 6 and 7), were unsuccessful and no polycarbonate formed (Figure S4). This finding was proposed to be caused by competitive coordination of ε-CL at the catalyst preventing copolymerization occurring by blocking epoxide binding. In order to understand the influence of CO₂ on ROP, the polymerization of ε-CL (600 equiv) was conducted, under a nitrogen gas atmosphere in the presence of CHO (2000 equiv), with the gas atmosphere exchanged to CO₂ after 36 min (Figure S5).

Analysis using in situ ATR-IR spectroscopy shows that shortly after CO₂ addition there is complete cessation of the polymerization, with the ε-CL conversion remaining at 70% by H NMR spectroscopy (Figure S6). The short time (~6 min) taken to completely stop polymerization likely corresponds to the rate of CO₂ dissolution. Indeed, using other related catalysts, if vacuum is applied prior to CO₂ addition, immediate cessation of polymerization occurred. Careful analysis of the polymer, using NMR spectroscopy, showed only PCL formation; there was no evidence for any CO₂ insertion into the polymer backbone (Figure S6). The zinc alkoxide intermediate, generated by reaction between 1 and CHO, immediately formed a new zinc carbonate species on exposure to just 1 bar pressure of CO₂ (as monitored by ATR-IR spectroscopy, Figure S1). Other researchers have also recently reported that CO₂ can be used to inhibit ROP of either ε-CL or cyclic carbonates, using quite different organocatalysts.

Thus, there is growing evidence that either metal or organic carbonate species are not viable initiators/catalysts for lactone ROP.

In order to shed light on the high degrees of selectivity observed experimentally, a DFT study was undertaken. It should be noted that the CHO/CO₂ ROCOP process using catalyst 1 has already been studied by DFT, therefore, the same level of theory was applied. For all calculations, the ωB97XD/6-31G(d)/SCRF (cpcm, solvent = dichloromethane) protocol was used. In fact, this protocol yields results in close agreement to those determined using higher basis sets (see Tables S7 and S8) and to those obtained using CCSD calculations; furthermore, the results are in excellent agreement with experimentally determined activation barriers. The calculations were conducted at the same temperatures as applied experimentally (ROP ε-CL, ROCOP CHO/CO₂ = 80 °C, and ROCOP PA/CHO = 100 °C). It is notable that there are very few theoretical studies of epoxide/CO₂ as yet there are none for epoxide/anhydride polymerizations. A recent

Table 1. Polymerizations Using Lactone, Epoxide, and CO₂

<table>
<thead>
<tr>
<th>run</th>
<th>1/CHO/ε-CL (equiv)</th>
<th>CO₂ (atm)</th>
<th>time</th>
<th>conv (%)</th>
<th>ε-CL</th>
<th>CHO</th>
<th>M₆ (g/mol)</th>
<th>M₆/M₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1/800/200</td>
<td>0</td>
<td>45 min</td>
<td>100</td>
<td>0</td>
<td>45.0</td>
<td>(1.90)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1/600/400</td>
<td>0</td>
<td>10 min</td>
<td>100</td>
<td>0</td>
<td>22.2</td>
<td>(1.50)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1/400/600</td>
<td>0</td>
<td>35 min</td>
<td>100</td>
<td>0</td>
<td>38.0</td>
<td>(1.4)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1/200/800</td>
<td>0</td>
<td>50 min</td>
<td>68</td>
<td>0</td>
<td>44.9</td>
<td>(1.4)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1/900/100</td>
<td>1</td>
<td>20 h</td>
<td>0</td>
<td>15</td>
<td>1.0</td>
<td>(1.08)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1/100/900</td>
<td>1</td>
<td>17 h</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1/400/600</td>
<td>1</td>
<td>8.5 h</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Reaction conditions: 1 = 1 equiv, 80 °C, monomer mixture as solvent. *Conversion determined by 1H NMR spectroscopy (see SI). *Determined by SEC, with polystyrene standards.

Figure 2. In situ catalyst activation for the ring-opening polymerization (ROP) of ε-CL.

Figure 3. Shows a plot of the PCL M₆ (black squares) and M₆/M₄ (blue dots) versus ε-CL conversion. Reaction conditions: 1/CHO/ε-CL = 1/600/2000, 80 °C.
Intermediate 6 can initiate $\epsilon$-CL ROP by a coordination/insertion mechanism (for the entire pathway see Figure S7), leading to the formation of intermediate $1^{12CL}$ (Figure 4). Coordination of $\epsilon$-CL forms intermediate $\gamma^{CL}$ ($\Delta G_{353} = -2.9$ kcal·mol$^{-1}$) and is followed by intramolecular attack on the lactone by the zinc alkoxide, leading to the hemi-acetal intermediate $9^{CL}$ ($\Delta G_{353} = -2.8$ kcal·mol$^{-1}$). The attack occurs via a relatively high energy transition state $8^{CHO-TS}$ ($\Delta G^\ddagger = +30.7$ kcal·mol$^{-1}$), in line with the reaction requiring temperatures above 80 °C to occur at an appreciable rate. Intermediate $9^{CL}$ is able to react further, by ring-opening of the hemi-acetal, leading to the formation of a new zinc alkoxide intermediate, $11^{CL}$ ($\Delta G = +9.4$ kcal·mol$^{-1}$). The ring-opening step occurs through a lower energy transition state $10^{CL-TS}$ ($\Delta G^\ddagger_{353} = +13.1$ kcal·mol$^{-1}$) involving acyl bond cleavage and zinc alkoxide bond formation. A slightly more stable intermediate $12^{CL}$ ($\Delta G_{353} = +2.5$ kcal·mol$^{-1}$) has a coordinative vacancy and is proposed as the intermediate for further propagations (Figure 4). Other groups have studied $\epsilon$-CL ROP, using DFT, and have isolated related transition states and found that the process may be exergonic.26

The alternative pathway, which is not observed experimentally, whereby intermediate 6 reacts with a second epoxide molecule, via a coordination/insertion pathway, was also considered (Figure 4, blue pathway). Accordingly, the barrier to epoxide ring-opening is significantly higher ($\Delta \Delta G_{353} = +39.1$ kcal·mol$^{-1}$ between $7^{CHO}$ and $8^{CHO-TS}$) compared to that for $\epsilon$-CL ring-opening ($\Delta \Delta G_{353} = +33.6$ kcal·mol$^{-1}$ between $7^{CL}$ and $8^{CL-TS}$). Nonetheless, the putative alkoxide intermediate formed by epoxide ring-opening would be stabilized ($\Delta G_{353} = -22.1$ kcal·mol$^{-1}$). In addition, the relative energies for the alternative copolymerization reactions, involving CO$_2$ and CHO, were considered (Figure 4, purple pathway). In line with the experimental findings, if CO$_2$ is present, the most

![Figure 4. Potential energy surface for activation and initiation in $\epsilon$-CL ROP (green), CHO/CO$_2$ ROCOP (purple), or CHO ROP (blue). (Full details are given in Table S3 and Figure S7; data are available at http://doi.org/10.14469/hpc/275.)](image-url)
favorable pathway is via CO$_2$ insertion, which has a significantly lower energy barrier ($\Delta \Delta G_{353} = +11.4$ kcal·mol$^{-1}$) and leads to a stable zinc carbonate intermediate $12CO_2$ ($\Delta G_{353} = -12.7$ kcal·mol$^{-1}$). There was no evidence that the zinc carbonate intermediate could subsequently insert an $\varepsilon$-CL molecule. Thus, the theoretical study is in line with the experimental observation that formation of a zinc carbonate prevents ROP.

The propagation pathway for $\varepsilon$-CL ROP leads to identification of various intermediates $12CL$–$17CL$ (Figure 5). The overall energies for the propagating species are lower than for the initiation species, and the energy decreases as polymerization progresses. Furthermore, the highest energy barrier, between $13$ and $14^{CL}$-TS ($\Delta G^{\ddagger} = +25.8$ kcal·mol$^{-1}$) is significantly lower than the equivalent barrier during initiation ($\Delta G_{353} = +33.6$ kcal·mol$^{-1}$). This is because the barrier to $\varepsilon$-caprolactone ring-opening depends on the nature of the metal alkoxide group: the secondary cyclohexylene alkoxide has a higher barrier than the primary alkoxide group. Such a difference is in line with the experimental observations that the rate of initiation ($k_i$) from the secondary alkoxide, cyclohexylene alkoxide is slower than that of propagation ($k_p$) from the primary alkoxide, caproyl alkoxide; the ratio of $k_i/k_p$ was determined to be 8. It was possible to experimentally further exploit the differences in activation barriers: thus, following polymerization of 100 equiv of $\varepsilon$-CL at 80 °C for 2.0 h, subsequent addition of $\varepsilon$-CL (100 equiv), at room temperature, led to formation of PCL (25 °C, 6.0 h), as observed by NMR and SEC analysis (the $M_n$ increases from 8.8 to 18.8 kDa; see Figures S9 and S10, and Table S5).

Other monomer coordination/insertion pathways were also compared. CO$_2$ inserts via a series of lower energy intermediates/transition states ($13CO_2$–$16CO_2$), leading to the formation of a significantly more stabilized zinc carbonate intermediate $18CO_2$ ($\Delta G_{353} = -9.6$ kcal·mol$^{-1}$). In addition to lower energy intermediates and transition states, the stabilization may, in part, explain the observed experimental selectivity whereby polymerizations conducted using mixtures of CHO, $\varepsilon$-CL, and CO$_2$ result only in the formation of polycarbonate. $18CO_2$ reacts further with CHO, leading to a new zinc alkoxide intermediate $21CO_2$ (see Figure S8). In contrast, it was not possible to locate a transition state for further reaction of $18CO_2$ with another lactone. These findings are consistent with the experimental observations that $\varepsilon$-CL remains unreacted during epoxide/CO$_2$ ROCOP and that addition of CO$_2$ “easily” switches to the formation of a carbonate intermediate. A further possible side reaction could be the insertion of CHO and thus sequential enchainment of epoxide (by ROP), leading to (poly)ether linkages (Figure 5, blue). However, the transition state for this transformation is likely too high to be accessible ($\Delta G^{\ddagger}_{353} = +42.7$ kcal·mol$^{-1}$), which may explain the lack of experimental evidence of such linkages.

**Lactone, Anhydride, and Epoxide Polymerizations.** Polymerizations from mixtures of anhydride, epoxide, and $\varepsilon$-CL were investigated (Figure 6). I can catalyze the ROCOP of phthalic anhydride (PA) and cyclohexene oxide (CHO). The polymerizations occur rapidly, forming perfectly alternating polyesters (>99% ester linkages) with very high selectivity (Table 2, run 1). In addition, it was already reported that I is a viable catalyst for $\varepsilon$-CL ROP, in the presence of epoxide. Thus, polymerizations from mixed feedstock of anhydride, epoxide, and $\varepsilon$-CL was investigated. The mixture polymerization, monitored using *in situ* ATR-IR spectroscopy,
proceeded highly selectively to give block copolyesters. First, the anhydride/epoxide ROCOP occurred (Figure 7), as evidenced by a decrease in resonances assigned to PA and by a concomitant increase in the semi-aromatic polyester absorption (PCHPE). During this phase (almost 2.5 h), there was no change in intensity of the resonances assigned to ε-CL, nor any evidence for PCL formation (by 1H NMR spectroscopy, by comparing the relative integrals of the signals assigned to PCHPE ester groups (5.16 ppm) compared with those assigned to PCL ester groups (4.07 ppm) in the copolymers. Calculated using the initial ratio of monomers.

To better understand the thermodynamic influences, DFT calculations were performed under the same conditions (Figure 9). To our knowledge, this is the first such theoretical study of polyester formation by ROCOP. The epoxide/anhydride copolymerization is conducted at slightly higher temperatures (100 °C), so intermediates 1–6 were re-optimised (intermediate 1′−6′) at the experimental temperature, leading to only minor changes in energy (Tables S3 and S6). From the common zinc alkoxide intermediate 6′, coordination of anhydride leads to intermediate 7PA (ΔG° = −1.6 kcal mol⁻¹). There are in fact, two enantiomeric approaches during the ring-opening of PA by the CHO alkoxide, and so two transition states for 8PA-TS (ΔG° = +11.7 kcal mol⁻¹) were found. Both structures and transition states are essentially isoenergetic, with almost identical activation barriers, and as both would lead to the same product after ring-opening, i.e., intermediate 12, only one pathway was studied further. The “forward” intrinsic reaction coordinate calculation from 8PA-TS (Figures S18 and S19) showed two hidden intermediates, 9PA and 10PA, leading to intermediate 11PA (ΔG° = −28.9 kcal mol⁻¹). These structures involve the ring-opening of the anhydride, followed by cleavage of the cyclohexyl Zn–O bond and coordination of the carboxylate oxygen at the other zinc center. These hidden intermediates are not true stationary points on the potential energy surface, as their first derivatives never quite approach zero, but can be thought of as frustrated minima which can only be characterized in the context of the IRC pathway. Intermediate 11PA is thermodynamically favored compared to the previous intermediates (ΔG° = −28.9 kcal mol⁻¹).

<table>
<thead>
<tr>
<th>run no.</th>
<th>1/CHO/PA/ε-CL (equiv)</th>
<th>Mₑ (P) b (kg mol⁻¹)</th>
<th>PCL linkages (%)</th>
<th>theor a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1/800/100/0</td>
<td>2.6 (1.42)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1/400/20/100</td>
<td>12.2 (1.42)</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>1/400/20/150</td>
<td>15.8 (1.43)</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>1/400/20/200</td>
<td>18.7 (1.57)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>1/400/10/150</td>
<td>22.5 (1.46)</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

The spectra show that ROCOP of PA/CHO occurs first (producing PCHPE), followed by ROP of ε-CL to produce a copolymer (PCHPE–PCL). Inset: enlarged spectra of the time period during which ε-CL ROP occurs. Reaction conditions: 1/CHO/PA/ε-CL = 1/400/20/200, 100 °C, monomer mixture as the solvent.
−28.9 kcal·mol⁻¹). Intermediate 12PA is stabilized (ΔG*TS = −14.1 kcal·mol⁻¹) and features a coordinative vacancy at the metal center, which is essential for forward polymerizations, for example leading to intermediate 13PA (ΔG*TS = −14.0 kcal·mol⁻¹). The latter undergoes intramolecular nucleophilic attack of the zinc carboxylate at the epoxide and proceeds via a transition state, 14PA−TS (ΔG*TS = 10.4 kcal·mol⁻¹). The overall energy barrier for CHO insertion (13PA, 14PA−TS) is expected to be inaccessible (ΔΔG*TS = +24.4 kcal·mol⁻¹) and leads to the formation of intermediate 15PA (ΔG*TS = −11.9 kcal·mol⁻¹), where a new zinc alkoxide bond is formed and a cyclohexylene oxide group has been inserted. Thus, the free energy profile for CHO/PA ROCOP is expected to be driven in part by the thermodynamic stability of some of the ring-opened intermediates.

The energy profile for epoxide/anhydride polymerization is also compared to the ROC of ε-CL (Figure 10). Starting from the common zinc alkoxide intermediate 6*, there is little energy difference between the coordination of the anhydride and lactone monomers. However, the energy barrier to ring-open the anhydride is significantly lower than that to open the lactone (ΔΔG*PA = +15.5 kcal·mol⁻¹ vs ΔΔG*ε-CL* = +34.4 kcal·mol⁻¹). Furthermore, when comparing the energy of the intermediate after ring-opening, 11PA* or 11CL*, it is clear that ROCOP results in a significantly lower energy intermediate (ΔG*PA = −23.2 kcal·mol⁻¹ vs ΔG*ε-CL = +15.2 kcal·mol⁻¹), signaling a thermodynamic driving force favoring ROCOP.

**Epoxide, Anhydride, and Carbon Dioxide Polymerizations.** Mixtures of CHO, PA, and CO₂ were polymerized selectively by catalyst 1 using ROCOP, to form only copoly(ester-carbonates). First, epoxide/anhydride co-polymerization occurred, until complete consumption of PA, after which point epoxide/CO₂ copolymerization occurred (Figures 8 and S2).

![Figure 8. Poly(ester-block-carbonate) formation from mixture of PA, CHO, and CO₂.](image)

Once again, the calculated energy profiles at 100 °C for both polymerizations were compared (Figure 11). From the common zinc alkoxide intermediate 6*, either PA or CO₂ is coordinated, leading to intermediates 7PA* and 7CO₂, respectively, which are of very similar energy. Next, insertion into the zinc alkoxide bond occurs (via transition states 8PA−TS and 8CO₂−TS, whose energies are less than 5 kcal·mol⁻¹ different). As stated, experimentally PA insertion occurs before CO₂ insertion, furthermore, CO₂ is not polymerized at all in the presence of PA. This could be attributed, in part, to the lower energy of intermediate 11PA, compared to 11CO₂. This energetic stabilization may be sufficient that CHO/PA ROCOP is essentially irreversible and therefore the dominant pathway of the two competing options.

**Comparison of Monomer Selectivity.** The dizinc catalyst shows unexpected chemoselectivity in polymerizations using different monomer mixtures yielding predictable compositions and block sequences in copolymers. The monomers are polymerized using two distinct catalytic cycles: the ring-opening copolymerizations (ROCO) of epoxides/CO₂ or epoxides/anhydrides and the ring-opening polymerizations (ROP) of lactones. It is feasible for one catalyst to bridge the two distinct cycles as both involve a zinc alkoxide intermediate (Scheme 1). Experimentally the preference for addition into the zinc–alkoxide bond follows the trend PA > CO₂ > ε-CL, and by exploiting this finding copoly(ester-carbonates) and copoly(esters) are formed (Scheme 2).

In order to understand and compare the elementary steps in the polymerization cycles, a series of DFT studies were undertaken considering two cycles of monomer additions and different permutations of the monomers. Common to all the polymerizations was the zinc alkoxide intermediate 6, generated by the reaction between the catalyst, zinc acetate, and an epoxide molecule. Figure 12 and Table 3 summarize the limiting energy barriers to the key transition states (ΔΔGTS) and the free energy differences (ΔG) between the corresponding intermediates in the various polymerization cycles.

**Epoxide/Anhydride/CO₂.** Of the combinations of monomers investigated, only mixtures of epoxides/anhydrides/CO₂ have been explored previously. In those studies, it was observed that various different types of homogeneous catalysts gave rise to high degrees of selectivity. Generally, the anhydride/epoxide ROCOP occurred prior to the CO₂/epoxide reaction. In the field of heterogeneous catalysis, there was much less discrimination between the monomers, with studies using zinc glutarate or zinc–cobalt double metal cyanides resulting in the formation of tapered or gradient block copoly(ester-carbonates). The rationale for the observed selectivity was always kinetic; i.e., it was argued that the rates of insertion of anhydride vs CO₂ into metal alkoxide intermediates determined the order of monomer enchainment. Here, it has been demonstrated that in addition to a kinetic rationale, there are also thermodynamic driving forces which could rationalize the experimental data. In particular, the ester linkage formed after anhydride insertion is significantly more thermodynamically stable compared to the carbonate linkage formed after CO₂ insertion. Furthermore, the calculated barriers for the insertions of either PA or CO₂ are not significantly different, particularly at the relevant temperatures for such reactions, to one another. These findings suggest that the observed selectivity in the terpolymerizations may result from a thermodynamic driving force toward formation of a more stable linkage.

**Lactone ROP and Epoxide/Anhydride or Epoxide/CO₂ ROCOP.** Mixtures of epoxides, lactones, and carbon dioxide result in selective formation of block copoly(ester-carbonates), whereby the CHO/CO₂ ROCOP occurs prior to the ε-CL ROP. The theoretical study shows a significantly higher barrier to ε-CL insertion, compared to CO₂, starting from the same zinc alkoxide intermediate. Furthermore, the product ester linkage is less stable compared to the carbonate linkage. Thus, in addition to kinetic phenomena governing the polymerization selectivity, the thermodynamic stability of the different linkages may also influence the observed selectivity. It is also notable that the initiation of the first ε-CL unit has a significantly higher barrier compared to subsequent propagation; this is because the initiation reaction involves attack by a secondary alkoxide compared to propagation occurring with attack by a primary alkoxide.

Polymerizations conducted using mixtures of epoxide/anhydride/lactone result in the selective formation of block
Figure 9. Calculated potential energy surface for ROCOP of CHO/PA that includes two hidden intermediates between $8^\text{PA-\,TS}$ and $11^\text{PA-}$. (Data are available at http://doi.org/10.14469/hpc/281.)

Figure 10. Polymerization pathways from mixtures of CHO, PA, and $\varepsilon$-CL. In red, the ROCOP of CHO/PA; in green, the ROP of $\varepsilon$-CL. (An interactive version of this figure is accessible online.)
Copolymers. The polymerizations progress by the ROCOP pathway until the anhydride is completely consumed, after which time the ROP pathway is accessible. The theoretical study reveals that there is a lower barrier to anhydride insertion, compared to ε-CL ROP, and a greater stability to the product ester linkage formed, thereby also providing a thermodynamic rationale for the observed selectivity.

The study also highlights the importance of considering both a kinetic and thermodynamic basis for future selective polymerizations. Nevertheless, it is also important to consider some other influences over catalytic selectivity. A notable observation is that the catalyst does not enchain epoxide units, and therefore ether linkages are barely detected. It could be concluded from this that sequential epoxide enchainment, by ROP, is not an experimentally accessible pathway, at least at
temperatures up to 100 °C. However, an examination only of the thermodynamic parameters, particularly during initiation, reveals that although the barriers to epoxide insertion are higher than for other monomers, there is a significant stability associated with the putative products. In contrast, during propagation, there is a much more significant difference in the energy barriers, with the epoxide enchainment requiring >10 kcal·mol⁻¹ more than the lactone enchainment.

Furthermore, the calculations do not provide kinetic models for initiation/propagation. It is difficult to directly measure the rates of monomer insertion into the zinc–alkoxide bond, particularly in the case of CO₂/anhydride as these are pre-rate-limiting reactions. A recent study of CO₂ insertion into a zinc hydride complex, featuring similar amine–phenolate ligands, revealed that the measured rate in fact corresponded with the rates of CO₂ dissolution/diffusion into the reaction medium (i.e., the reaction was diffusion limited). Given that the rate observed in that study was typical of other zinc complexes reported for CO₂ insertion processes, it seems likely that related insertion reactions may also occur under diffusion-limited conditions. Another factor which would be expected to influence the order of monomer insertion is the concentration of the particular monomer coordinated intermediate. The coordination of the relevant monomer to the catalyst is likely an equilibrium process which would be affected by the relative concentrations of monomers. In the current study, a range of

\[ aT = 373.15 \text{ K.} \quad bT = 273.15 \text{ K.} \]
different loadings have been explored, and, in most cases, the concentration of the epoxide was significantly greater than that of any other species present. This might be expected to bias somewhat the concentration of the epoxide-coordinated intermediate and thereby enable epoxide enchainment; however, this was never observed experimentally. Finally, it might be expected that if polymerizations could be run at significantly higher temperatures the apparent barrier to epoxide enchainment could be overcome. This is not practical experimentally due to competing factors: (1) ROCOP is an equilibrium process, where in the case of CO₂/epoxide ROCOP the polymer is the kinetic product, and thus elevated temperatures lead to back-biting and formation of the cyclic carbonate. (2) ROP is also an equilibrium process, and elevated temperatures lead to the back-reaction and increase monomer concentration/polymer degradation. Thus, the epoxide enchainment reaction does not occur using the dizinc catalysts under any of the experimentally studied conditions. This may relate to relatively higher barriers, particularly during propagation, but is not immediately disfavored by the theoretical study. It is interesting to note that various other homogeneous metal complexes have been reported to enchain epoxide units as well as carbonates/esters; thus, there appear to be different influences of the relative barriers/rates which depend on the metal catalysts selected.\(^{12,13}\)

## CONCLUSIONS

Selecting monomers from a mixture so as to construct complex (multi-block) copolymers is a long-standing challenge in polymer chemistry. Usually, copolymer composition is predicted on the basis of empirical monomer reactivity ratios. In this study, a new catalytic approach where a single catalyst can switch between different polymerization cycles and mechanisms enables the selective preparation of copolymers from mixtures of four different monomers. The catalysis is explored using both experimental and DFT studies of all possible monomer combinations using ε-caprolactone, phthalic anhydride, carbon dioxide, and cyclohexene oxide. Block copolyesters and copoly(ester-carbonates) are selectively formed experimentally, and the DFT study reveals that the more stable intermediates (linkages) in the polymerization pathways. The findings are important as previous attempts to rationalize selective behavior have only considered kinetic phenomena. Given the applications and fundamental interest in block copolymers and degradable, oxygenated polyesters/carbonates, this study has broader implications. In particular, the investigation of other catalysts and other monomer combinations is certainly warranted, and with the detailed understanding of the factors controlling the selectivity in hand it is appropriate to apply this knowledge to prepare more complex and sophisticated polymer architectures.

## ASSOCIATED CONTENT

© Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13070. Complementary data are available from the Imperial College High Performance Computing Service Data Repository at http://doi.org/10.14469/hpc/244.

Experimental procedures and spectroscopic characterization, including Figures S1–S33 and Tables S1–S8 (PDF)

## Web-Enhanced Features

Interactive versions of Figures 10 and 11 are accessible in the HTML version of the article.

## AUTHOR INFORMATION

### Corresponding Authors

* c.romain@imperial.ac.uk
* c.k.williams@imperial.ac.uk

### Notes

The authors declare the following competing financial interest(s): C.K.W. is a director at Econic Technologies.

## ACKNOWLEDGMENTS

The EPSRC (EP/K035274/1, EP/L017393/1, EP/K014070/1, EP/K014668/1), Roger and Sue Whorrod (fellowship to A.B.), and the CSC (studentship to Y.Z.) are acknowledged for research funding. We thank Imperial College London HPC and EPSRC NSCCS (CHEM826) for computing resources.

## REFERENCES

(c) Darenbourg, D. J.; Poland, R. R.; Escobedo, C. Macromolecules 2012, 45, 2242–2248.
(12) (a) Bernard, A.; Chatterjee, C.; Chisholm, M. H. Polymer 2013, 54, 2639–2646.