

# Understanding the phosphoric acid catalysed ring opening polymerisation of -Butyrolactone and other cyclic esters



# Understanding the phosphoric acid catalysed ring opening polymerisation of β-butyrolactone and other cyclic esters

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**Abstract:**

A series of phosphoric acid derivatives have been synthesised and their catalytic activity in the ring opening polymerisation of β-butyrolactone (β-BL), ε-caprolactone and *rac*-lactide probed. Improved synthetic protocols and characterisation data are provided for a range of catalysts substituted with functional groups altering their electron density and $pK_a$. Lower rates are observed for β-BL polymerisations than other aliphatic cyclic esters. By exploring the reaction kinetics and *in situ* NMR spectroscopy, we show that the activity decreases due to competitive formation of an off-cycle deactivated species through cleavage of catalyst P-O bonds.

**Keywords: Organocatalyst, β-butyrolactone, cyclic esters, catalyst deactivation, phosphoric acids.**

## 1. Introduction

The chemical and biological resistance of many modern plastics highlight environmental concerns that compete against the versatility and low cost of these materials. The development of biodegradable polyesters such as poly(lactic acid), poly(ε-caprolactone and poly(3-hydroxybutyrate) (PHB) provides a potential solution. While PHB, in particular, can be prepared directly by bacteria, processing problems from fermenting conditions have led to significant exploration of synthetic strategies for its synthesis. Catalytic ring opening polymerisation (ROP) of this monomer is usually mediated by organometallic, Lewis acidic catalysts, raising toxicity and cost concerns. Fortunately, metal free organocatalysts are becoming increasingly popular in ROP,[1-9] and are highly desirable in biomedical and electronics applications.[10]

In particular, Brønsted acids have garnered significant attention as ROP catalysts.[11, 12] Many organic reactions, including ROP, are catalysed via carbonyl activation; an efficient way to activate this bond is with these Brønsted acids.[13-19] Phosphoric acids not only contain an acidic proton, but also a phosphoryl oxygen that can act as a hydrogen bond acceptor, adding potential to act as dual activating catalysts. Despite this dual activating ability, these catalysts remain understudied compared to the more celebrated organocatalysts 1,8-diazabicycloundec-7-ene (DBU) and triazabicyclodecene (TBD). Bourissou and coworkers demonstrated that phosphoric acids can control the ROP of ε-caprolactone with dispersities (Đ) as low as 1.06 with molecular weights up to 15,000 gmol-1. Computational investigations suggested a transition state for propagation where the catalyst activates both the initiator and monomer, supporting bifuncationality.[20] Kakuchi and coworkers also reported diphenyl phosphate as a potential catalyst for ε-caprolactone and δ-valerolactone polymerisation, including kinetic studies showing good control up to 24 h,[21] and binapthol phosphoric acids that catalysed the stereoselective ROP of lactide.[22] Chakraborty and coworkers claimed to have synthesised substituted phosphoric acids and showed that electron

withdrawing halogen substituents improved activity in ε-caprolactone polymerisations.[23] Hillmyer reported using diphenyl phosphate as a catalyst with a wide range of alkyl-substituted δ-valerolactones.[24] The only report of β-butyrolactone (β-BL) polymerisation involves diphenyl phosphate and bis(p-nitrophenyl)phosphate,[25] with the electron deficient nitro containing catalyst again showing higher activity. The unsubstituted variant was further limited to low monomer loadings, suggested to be due to lower catalyst acidity. We were intrigued by the lack of success with β-BL compare to cyclic esters with less ring strain to drive ring opening, and wanted to explore why this monomer was so unusually challenging.

This communication looks closely at how these types of catalysts behave with β-BL compared to ε-caprolactone and *rac*-lactide, expands the scope of catalysts explored with these monomers, and explores the potential deactivation pathways available with the smaller ring of β-BL. Modification of the catalyst can prevent this deactivation pathway, accessing controlled ROP of β-BL by phosphoric acid catalysts. While important for polymerisation catalysis, these insights may additionally guide small molecule catalytic transformations with phosphinic acid organocatalysts.

## 2. Experimental

### 2.1 Procedures and Materials

All reactions were carried out under an inert atmosphere using standard Schlenk or glovebox techniques, unless stated otherwise. Phosphoric acid $pK_a$ values were determined by titrating a 0.1 M of the acid in 10:1 v/v IPA/ methanol against a tetrabutylammonium hydroxide solution (0.1M, 10:1 v/v IPA/methanol). Toluene was obtained from an Innovative Technologies solvent purification system and lyophilised three times before use. 3-Phenyl-1-propanol, *rac*-β-butyrolactone, $d_8$-THF and $d_8$-toluene were obtained from Sigma Aldrich,

dried over $CaH_2$ and distilled prior to use and stored under 3Å molecular sieves. Phenol was purchased from Sigma Aldrich and recrystallized from chloroform. ε-Caprolactone was purchased from Fisher Scientific, dried over $CaH_2$ and distilled prior to use. *rac*-Lactide was obtained from Purac and sublimed 3 times before use. Phosphorus oxychloride, lithium chloride, 4-cyanophenol, 3-chlorophenol, 3-(trifluoromethyl)phenol and bis(4-nitrophenyl)phosphate were purchased from Sigma Aldrich and used as received. 4-Methyloxyphenol and 4-(trifluoromethyl)phenol were purchased from Merck and used as received. 3-Cyanophenol was purchased from Alfa Aesar and used as received. 4-Tert-butylphenol was purchased from Fisher and used as received. 4-Chlorophenol was purchased from Fluka and used as received.

### 2.2 Measurements

$^{1}H$ NMR spectra were recorded using BrukerAsance (400 or 500 MHz) spectrometers and referenced to tetramethylsilane. $^{13}C\{^{1}H\}$ NMR spectra were recorded using a Bruker Asance (at 126 MHz) spectrometer and referenced to tetramethylsilane. $^{31}P\{^{1}H\}$ NMR spectra were recorded using a BrukerAsance (at 202 MHz) spectrometer referenced to 80% $H_3PO_4$. UV/vis spectra were obtained as DMSO solutions in 1 cm glass cuvettes using a Shimadzu UV-1800 UV spectrophotometer at room temperature. Electrospray Ionisation Fourier Transform Mass Spectrometry (ESI MS) measurements were recorded in positive and negative ion-mode using the standard Bruker ESI sprayer operated in “infusion” mode coupled with SolariX FTICR mass spectrometer. Direct infusion spectre were typically 10 acquisitions. All mass spectra were analysed using DataAnalysis software version 4.1 SR1 build 362.7 (Bruker Diagnostics). Ions were assigned manually. Infrared spectra were recorded with solid samples

on a Perkin Elmer spectrum 65 FT-IR spectrometer. Gel permeation chromatography (GPC) was conducted in THF at a flow rate of 1 mL/min on a Malvern Instruments Viscotek 270 equipped with triple detection using THF as the eluent at room temperature and additionally calibrated by polystyrene standards.

### 2.3 Catalyst Synthesis

The general procedure for the synthesis of phosphoric acid catalysts is as follows: The desired phenol (0.019 mol, 4-methoxyphenol, 4-cyanophenol, 3-chlorophenol, 4-chlorophenol, 3-(trifluoromethyl)phenol, 4-(trifluoromethyl)phenol, 3-cyanophenol or 4-tert-butylphenol), phosphorous oxychloride (0.019 mol) and lithium chloride (0.24 mmol) were combined in a Schlenk tube and heated to 110°C for 24 h. After allowing the reaction mixture to cool to room temperature, water (10 mL) was added slowly and the reaction subsequently reheated to 90°C for 16 h. The organic layer was extracted with dichloromethane. The product was then extracted using an aqueous sodium carbonate solution. The basic solution was neutralised with an aqueous hydrochloric acid solution and the product extracted using DCM and dried in vacuo. The resulting solid was then dried under high vacuum for 18 hours.

For example: 4-methyloxyphenol (2.38 g, 0.019 mol), phosphorus oxychloride (2.89 g, 0.019 mol) and lithium chloride (0.01 g, 0.24 mmol) were heated to 110°C in a Schlenk tube for 24 h. The mixture was allowed to cool to rt and a crude NMR taken. The mixture was then used without purification. Water (10 mL) was added and the reaction mixture was heated to 90°C for 16 h. The organic layer was extracted with dichloromethane. The product was then extracted using an aqueous 1M sodium carbonate solution (20 mL). The basic solution was neutralised with an aqueous 1M hydrochloric acid solution and the product extracted using DCM and dried in vacuo. The resulting solid was then dried under high vacuum for 18 hours.

Characterisation data: Catalyst **1** Yield: 3.42 g (58%). $^{1}$H NMR ($CDCl_3$, ppm): δ7.10 (dd, J = 9.1, 1.2 Hz, 4H), 6.83 (d, J = 9.0 Hz, 4H), 3.79 (s, 3H). $^{13}$C {$^{1}$H} NMR ($CDCl_3$, ppm) δ156.95, 143.97 (d, $^{2}J_{CP}$ = 7.4 Hz), 121.06 (d, $^{3}J_{CP}$ = 4.6 Hz), 114.63, 55.57. $^{31}$P {$^{1}$H} NMR ($CDCl_3$, ppm): δ-8.63. FTIR ($cm^{-1}$): 1216 (P=O). MS ($[M-H]^-$) m/z) calculated: 309.06, found: 309.05.

**2** Yield: 4.23 g (61%). $^{1}$H NMR ($CDCl_3$, ppm): δ7.33 (d, J = 8.6 Hz, 4H), 7.12 (dd, J = 8.8, 1.04 Hz, 4H), 1.31 (s, 18H). $^{13}$C {$^{1}$H} NMR ($CDCl_3$, ppm) δ148.16 (d, $^{2}J_{CP}$ = 4.1 Hz), 126.53, 119.50 (d, $^{3}J_{CP}$ = 4.4 Hz), 110.92, 34.38, 31.37. $^{31}$P {$^{1}$H} NMR ($CDCl_3$, ppm): δ-9.04. FTIR ($cm^{-1}$): 1210 (P=O). MS ($[M-H]^-$) m/z) calculated: 361.17, found: 361.16.

**3** Yield: 2.08 g (43%). $^{1}$H NMR ($CDCl_3$, ppm): δ7.30 (t, J = 8.3, 4H), 7.20-7.14 (m, 6H). $^{13}$C {$^{1}$H} NMR ($CDCl_3$, ppm) δ150.39 (d, $^{2}J_{CP}$ = 7.0 Hz), 129.72, 125.40, 120.16 (d, $^{3}J_{CP}$ = 5.0 Hz). $^{31}$P {$^{1}$H} NMR ($CDCl_3$, ppm): δ-10.24. FTIR ($cm^{-1}$): 1220 (P=O). MS ($[MH]^+$) m/z) calculated: 251.05, found: 251.05.

**4** Yield: 3.37 g (56%). $^{1}$H NMR ($CDCl_3$, ppm): δ7.30 (d, J = 8.8 Hz, 4H), 7.10 (d, J = 8.2 Hz, 4H). $^{13}$C {$^{1}$H} NMR ($CDCl_3$, ppm) δ148.63 (d, $^{2}J_{CP}$ = 7.2 Hz), 131.20, 129.88, 121.46 (d, $^{3}J_{CP}$ = 5.0 Hz). $^{31}$P {$^{1}$H} NMR ($CDCl_3$, ppm): δ-10.03. FTIR ($cm^{-1}$): 1237 (P=O). MS ($[MH]^+$) m/z) calculated: 318.97, found: 318.97, ($[M-H]^-$) m/z) calculated: 316.95, found: 316.96.

**5** Yield: 2.98 g (49%). $^{1}$H NMR ($CDCl_3$, ppm): δ7.24 (dd, J = 8.2, 0.7 Hz, 2H), 7.19-7.17 (m, 2H), 7.08 (dt, J = 2.3, 1.2 Hz, 2H), 7.06 (dt, J = 2.3, 1.2 Hz, 2H). $^{13}$C {$^{1}$H} NMR ($CDCl_3$, ppm) δ150.52 (d, $^{2}J_{CP}$ = 7.1 Hz), 135.10, 130.53, 126.02, 120.83 (d, $^{3}J_{CP}$ = 5.4 Hz), 118.39 (d, $^{3}J_{CP}$ = 4.9 Hz). $^{31}$P {$^{1}$H} NMR ($CDCl_3$, ppm): δ-12.60. FTIR ($cm^{-1}$): 1260 (P=O). MS ($[M-H]^-$) m/z) calculated: 316.95, found: 316.95.

**6** Yield: 3.81 g (52%). $^{1}$H NMR ($CDCl_3$, ppm): δ7.50-7.43 (m, 4H), 7.42 (s, 2H), 7.40-7.35 (m, 2H). $^{13}$C {$^{1}$H} NMR ($CDCl_3$, ppm) δ150.12 (d, $^{4}J_{CP}$ = 7.4 Hz), 132.57 (q, $^{1}J_{CF}$= 32.8 Hz), 130.52, 124.30, 123.47 (d, $^{3}J_{CP}$ = 4.9 Hz), 122.48, 117.37 (d, $^{3}J_{CP}$ = 5.0 Hz). $^{31}$P {$^{1}$H} NMR ($CDCl_3$, ppm): δ-11.20. FTIR ($cm^{-1}$): 1234 (P=O). MS ($[MH]^+$) m/z) calculated: 387.02, found: 387.02.

**7** Yield: 3.52 g (48%). $^{1}$H NMR ($CDCl_3$, ppm): δ7.64 (d, J = 8.4 Hz, 4H), 7.33 (d, J = 8.5 Hz, 4H). $^{13}$C {$^{1}$H} NMR ($CDCl_3$, ppm) δ152.24 (d, $^{2}J_{CP}$ = 7.35 Hz), 132.75 (d, $^{3}J_{CP}$ = 4.3 Hz), 127.35 (q, $^{1}J_{CF}$ = 32.7 Hz), 122.29 (d, J = 3.9 Hz), 120.48, 115.54. $^{31}$P {$^{1}$H} NMR ($CDCl_3$, ppm): δ-10.52. FTIR ($cm^{-1}$): 1236 (P=O). MS ($[M-H]^-$) m/z) calculated: 385.01, found: 385.00.

**8** Yield: 3.98 g (70%). $^{1}$H NMR ($CDCl_3$, ppm): δ7.36 (t, J = 8.0 Hz, 2H), 7.24 (dt, J = 7.7, 1.2 Hz, 2H), 7.16 (t, J = 2.0 Hz, 2H), 7.13 (dd, J = 8.3, 2.6, 2H). $^{13}$C {$^{1}$H} NMR ($CDCl_3$, ppm) δ156.33 (d, $^{2}J_{CP}$ = 6.6 Hz), 131.11, 129.33, 125.15 (d, $^{3}J_{CP}$ = 4.7 Hz), 123.72, 118.58, 113.69. $^{31}$P {$^{1}$H} NMR ($CDCl_3$, ppm): δ-11.66. FTIR ($cm^{-1}$): 1226 (P=O). MS ($[M-H]^-$) m/z) calculated: 299.02, found: 299.02.

**9** 3.98 g (70%). $^{1}$H NMR ($CDCl_3$, ppm): δ7.33 (t, J = 7.3, 4H), 7.19 (m, 4H). $^{13}$C {$^{1}$H} NMR ($CDCl_3$, ppm) δ150.41 (d, $^{2}J_{CP}$ = 7.3 Hz), 129.71, 125.36, 120.17 (d, $^{3}J_{CP}$ = 4.9 Hz), 117.81. $^{31}$P {$^{1}$H} NMR ($CDCl_3$, ppm): δ-9.48. FTIR ($cm^{-1}$): 1249 (P=O). HRMS ($[MH]^+$) m/z) calculated: 301.04, found 301.04. MS ($[M-H]^-$) m/z) calculated: 299.02, found: 299.02.

Representative polymerisation: All polymerisations were set up in a glovebox. For a β-butyrolactone polymerisation, a solution of β-butyrolactone (0.019 g, 0.22 mmol), 3-phenyl-1-propanol (0.0030 g, 0.022 mmol) and catalyst **1**-**9** (0.022 mmol) were prepared in toluene

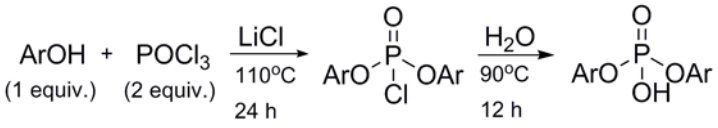
(2 mL). The mixture was stirred at 100°C for 24 h. A crude NMR was taken and the polymerisations quenched by precipitation into cold hexane.

Representative kinetic polymerisation: All kinetic polymerisations were set up in the glovebox. A solution of β-butyrolactone (0.010 g, 0.12 mmol), 3-phenyl-1-propanol (0.0016 g, 0.012 mmol) and catalyst **1**-**9** (0.012 mmol) were made up in $d_8$-toluene (0.70 mL). The sample was kept at 100°C in the magnet for 24 hr. A $^{1}$H NMR spectrum was taken every 20 mins and an $^{31}$P{$^{1}$H} NMR spectrum recorded every 60 min.

## 3. Results and Discussion

### 3.1 Synthesis and Characterisation of Polyphosphonates

A series of phosphoric acid derivatives were synthesised as shown in Scheme 1. As the acidity of the catalyst will play an important role in catalysis, the p$K_a$'s of **1**-**10** were experimentally determined and are found in Table 1. As expected, the acidity increases with the electron-withdrawing capacity of the aromatic substituent(s), except for the surprising cyano-containing catalysts which have much higher p$K_a$ values than expected. It is possible that the cyano groups have become protonated so these two catalysts are now less acidic.




Ar = *p*-$OMeC_6H_4$, **1**; *p*-$^tBuC_6H_4$, **2**; $C_6H_5$, **3**; *p*-$ClC_6H_4$, **4**; *m*-$ClC_6H_4$, **5**; *m*-$CF_3C_6H_4$, **6**; *p*-$CF_3C_6H_4$, **7**; *m*-$CNC_6H_4$, **8**; *p*-$CNC_6H_4$, **9**; *p*-$NO_2C_6H_4$, **10**.

**Scheme 1:** The synthesis of phosphoric acids **1**-**10**.

**Table 1:** Phosphoric acids synthesised and their p$K_a$s

| Catalyst | *m* | *p* | σ | p$K_a$ [b] |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **1** | H | OMe | -0.27 | 4.83 |
| **2** | H | $^{t}$Bu | -0.20 | 4.00 |
| **3** | H | H | 0.00 | 3.05 |
| **4** | H | Cl | 0.23 | 2.13 |
| **5** | Cl | H | 0.37 | 2.04 |
| **6** | $CF_3$ | H | 0.43 | 1.95 |
| **7** | H | $CF_3$ | 0.54 | 1.60 |
| **8** | CN | H | 0.56 | 2.95 |
| **9** | H | CN | 0.66 | 2.33 |
| **10**[a] | H | $NO_2$ | 0.78 | 0.75 |

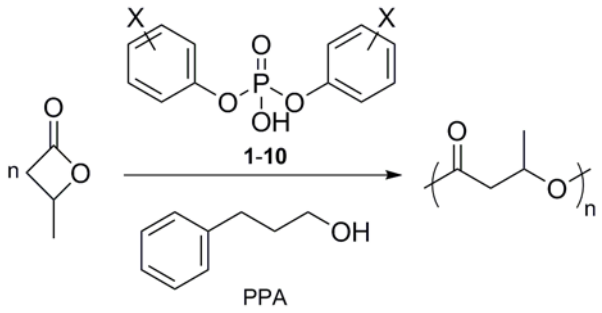
[a] catalyst 10 commercially sourced. [b] determined by the half-equivalent point by titration at ambient temperature

These optimised synthetic conditions differ from those previously reported.[23] Following the reported conditions instead affords triaryl phosphoric acid that match the published spectroscopy data, suggesting incorrect assignments or reported conditions. However, under our new conditions where the stoichiometry has been altered, the substituted phosphoric acids are readily accessible. In all cases, spectroscopic characterisation was consistent with the expected resonances across $^{1}$H, $^{13}$C and $^{31}$P NMR spectroscopy (see Supplementary Material).

### 3.2 Ring opening polymerisations of β-butyrolactone

The unsubstituted diphenyl phosphoric acid catalyst was screened in β-BL ROP, as shown in Scheme 2, with results shown in Table 2. The polymerisation occurs in the absence of an initiator (entry 1) at elevated temperatures, with the catalyst hydroxyl likely serving this role.

Even with 3-phenylpropan-1-ol (PPA) as an initiator, no polymerisation occurs at room temperature. Polymerisations remain sluggish at 80, 100 and 120 °C. Surprisingly, conversion did not improve with increasing reaction times. At higher monomer concentrations, polymerisation is inhibited. This behaviour contrasts strikingly with the ROP of with ε-caprolactone and *rac*-lactide, with conversions of 80 and 84% respectively were obtained, in agreement with previously published results.[20, 22] As electron withdrawing power increases on the substituent (entries 9-17), a clear and expected increase in conversion is observed. Molecular weight determination by mass spectrometry revealed an initiator residue at the chain end, confirmed the oligomers formed are linear. The spectrum of the reaction mixture produced with catalyst **4** is shown in the ESM (Figure S10). When catalyst **10** was used at a lower catalyst loading (entry 18) a dispersity of 1.20 was obtained showing a reasonable level of control, similar to that previously reported.[25]




**Scheme 2:** Scheme of ROP of β-BL where PPA is phenyl-1-propanol.

**Table 2:** Screening conditions for ROP of β-BL catalysed by diphenyl phosphoric acid

| Entry | Cat. | Int. | Ratio[a] | Time / hr | Temp / °C | Conversion / %[b] | Mn[c] |
|---|---|---|---|---|---|---|---|
| 1 | 3 | none | 10:1:1 | 24 | 100 | 42 | n.d.[d] |
| 2 | 3 | PPA | 10:1:1 | 24 | rt | 0 | n.d.[d] |
| 3 | 3 | PPA | 10:1:1 | 24 | 80 | 34 | n.d.[d] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 4 | 3 | PPA | 10:1:1 | 24 | 100 | 56 | 571 |
| 5 | 3 | PPA | 10:1:1 | 24 | 120 | 55 | n.d.[d] |
| 6 | 3 | PPA | 10:1:1 | 60 | 100 | 48 | n.d.[d] |
| 7 | 3 | PPA | 100:1:1 | 24 | 100 | 9 | n.d.[d] |
| 8 | 3 | PPA | 50:1:1 | 24 | 100 | 23 | n.d.[d] |
| 9 | 1 | PPA | 10:1:1 | 24 | 100 | 34 | 434 |
| 10 | 2 | PPA | 10:1:1 | 24 | 100 | 31 | 470 |
| 11 | 4 | PPA | 10:1:1 | 24 | 100 | 63 | 710 |
| 12 | 5 | PPA | 10:1:1 | 24 | 100 | 64 | 714 |
| 13 | 6 | PPA | 10:1:1 | 24 | 100 | 65 | 653 |
| 14 | 7 | PPA | 10:1:1 | 24 | 100 | 68 | 726 |
| 15 | 8 | PPA | 10:1:1 | 24 | 100 | 75 | 765 |
| 16 | 9 | PPA | 10:1:1 | 24 | 100 | 86 | 825 |
| 17 | 10 | PPA | 10:1:1 | 24 | 100 | >99 | 980 |
| 18 | 10 | PPA | 100:1:1 | 16 | 100 | 88 | 7500 |

[a] [Mon]:[Int]:[Cat], [b] determined by $^{1}$H NMR, [c] molecular weight determined by $^{1}$H NMR, [d] not determined as these entries were for polymerisation optimisation only.

To confirm the dual activating nature of the catalysts we examined the interaction of *rac*-ethyl 3-hydroxybutyrate with catalysts **1**-**10**, ([*rac*-ethyl 3-hydroxybutyrate]/[cat] = 0.5, in $d_8$-THF at 500 MHz). Figure 1 shows a representative shift (3.82 ppm to 4.23 ppm) and change in multiplicity (doublet to singlet) of the hydroxyl proton upon mixing the catalyst with this model chain end, supporting an interaction with the phosphoryl oxygen. This technique has previously been used to indicate chain-end activation,[25] however, it is possible this phenomenon is due to proton exchange between the alcohol and phosphoric acid hydroxyl groups. Similarly, the activation of the carbonyl in the monomer was monitored by $^{13}$C{$^{1}$H}

NMR spectroscopy ([B-BL]/[cat] = 0.5, in $d_8$-THF at 126 mHz). Upon mixing monomer and catalyst, the carbonyl resonance shifts upfield. The magnitude of these shifts in both $^{1}H$ and $^{13}C\{^{1}H\}$ NMR resonances correlates with the electron deficiency of the catalyst (see Table S1).

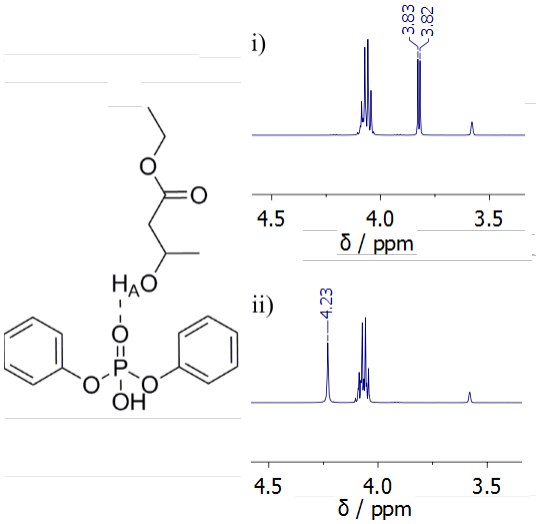



**Figure 1:** $^{1}H$ NMR spectrum of ethyl 3-hydroxybutyrate i) before and ii) after mixing with catalyst **2** (in $d_8$-THF).

### 3.3 Kinetic and deactivation studies

With confirmation of dual activating catalysts with this monomer, we investigated polymerisation kinetics to shed light on the observed low conversions. Specifically, reaction rates for the initial 4 hours for each catalyst were measured (Table S2) with rates correlating well with the Hammett substituent constants (σ[26, 27]) for the catalysts (Figure 2).

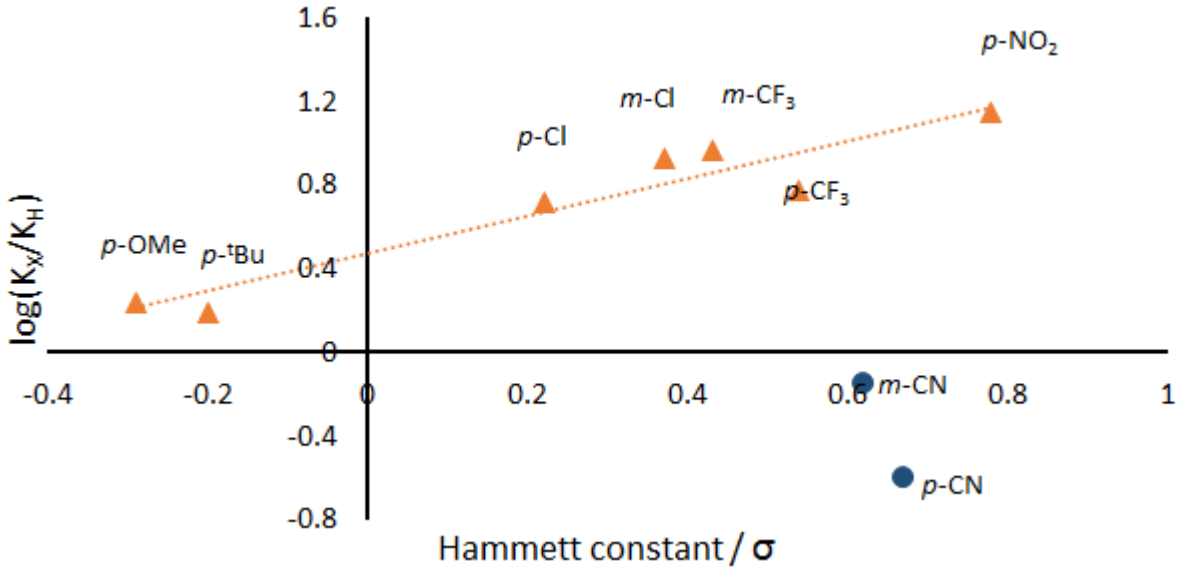



**Figure 2:** Hammett plot of phosphoric acid catalysts.

Discounting catalysts **8** and **9**, a strong correlation is present between observed rates and Hammett constant (σ). The gradient of the orange trend line (ρ) has a value of 0.90. A positive ρ suggests an increase in electron density in the transition state of the rate determining step. This is expected when the rate determining step involves donation of a proton; more specifically as $\rho < 1$, the acidic moiety is likely not delocalised with the benzene ring. For an acidic moiety 3 bonds away from the benzene ring, a ρ of 0.5 would be expected; the higher ρ value observed provides additional support for catalyst bifunctionality. Interestingly, the rates of catalysts **8** and **9** are considerably slower than expected – these are the two cyano containing catalysts that had significantly higher $pK_a$ values than expected. As they are weaker acids, the monomer activation in the rate determining step is hindered, leading to a lower observed rates. However, these reactivity trends do not entirely explain why the ROP of β-BL is so challenging.

Extending this kinetic study to a full 24 hours begins to illuminate the problem. Figure 3 shows the kinetic profile for catalyst **4**, representative of reactions catalysed by **1**-**9** (Figures

S11-19). The plot deviates significantly from linearity, with the rate dropping significantly after 4h.

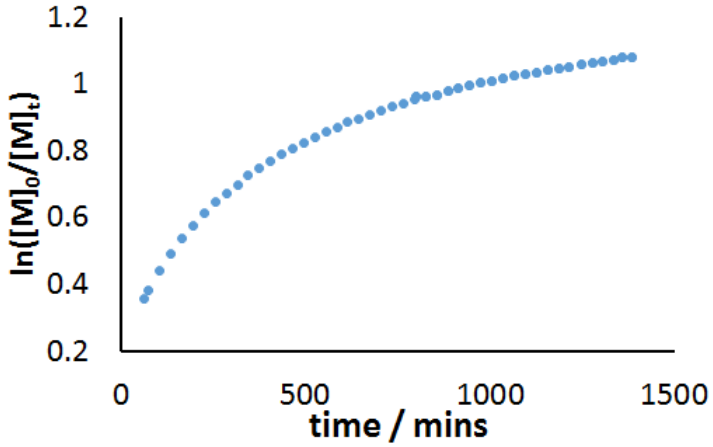



**Figure 3:** Kinetic profile of catalyst **4**.

Hillmyer and coworkers previously reported a non-first order dependence on monomer concentration for similar catalysts,[24] where rate increases with conversion, conversely to what is seen here. This occurs where the monomer is more basic than the polymer.[28] In a separate publication Hillmyer again saw a derivation from linearity with this type of catalyst, this time with a concave down slope as seen here, though, no further investigation was carried out to identify the reason.[29] To test whether a potential change in rate determining step or catalyst decomposition was the cause, a second aliquot of monomer was added after 1000 min to the original monomer concentration. With an original rate of 0.0011 $mins^{-1}$, the rate after addition of the second aliquot had decreased to 0.0005 $mins^{-1}$, confirming a significant proportion of the catalyst had transformed into a deactive or poorly active species. At these harsh conditions crontonation can occur which can aid deactivation. However, no vinyl signals were detected in the $^{1}H$ NMR spectrum of the reaction mixture, a zoomed in spectrum can be found in the ESM (Figure S20). Monitoring the reaction by $^{31}P\{^{1}H\}$ NMR spectroscopy shows the immediate formation of a prominent peak at the beginning of the reaction (-16.66 ppm, **A**), likely the active form of the catalyst, and the slow growth of a

second species (-18.12 ppm, **B**) that we suggest is the deactivated species. As the reaction progresses, conversion of **A** into **B** is observed, with the relative integration of these peaks correlating with the observed rate profile (Figure 4).

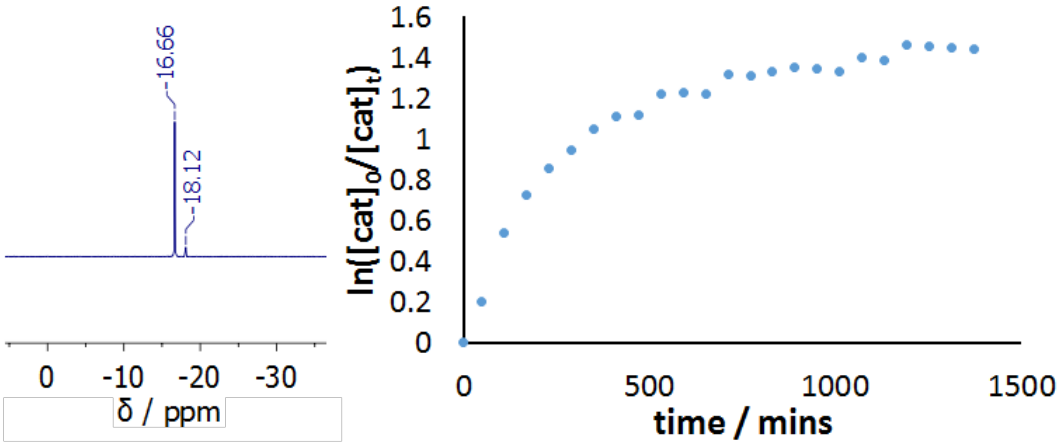



**Figure 4:** i) $^{31}P\{^{1}H\}$ NMR spectrum once polymerisation has started and ii) kinetic plot of active catalyst.

To characterise the nature of this deactivated species, $^{1}H/^{31}P$ HMBC NMR spectra were examined during the polymerisations of β-BL, ε-caprolactone and *rac*-lactide (Figure 5).

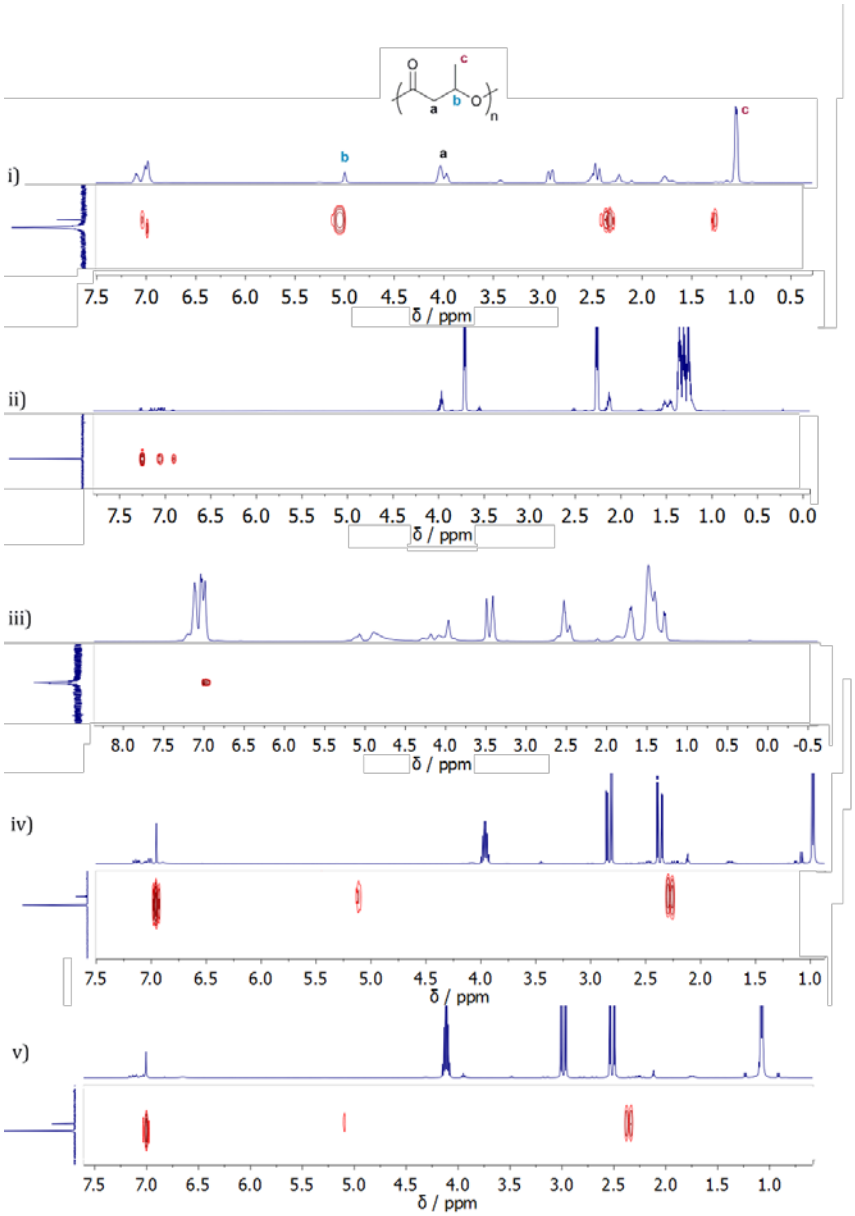



**Figure 5:** $^{1}H/^{31}P$ HMBC NMR spectra of polymerisations with i) β-BL, ii) ε-caprolactone, iii) *rac*-lactide with catalyst **4**, iv) β-BL at [50]:[1]:[1] and v) β-BL at [100]:[1]:[1].

No such deactivated species is observed in the ROP of ε-caprolactone or *rac*-lactide. In β-BL polymerisations, this deactivated species $^{31}P$ nucleus couples to fragments similar to the hydroxybutyrate monomer unit, suggesting incorporation of a monomer fragment unique to

this smaller ring unit. This deactivated species is also formed at higher monomer loadings, at 50:1:1 and 100:1:1, the same $^{31}$P NMR signal is detected (Figure 5 iv) and v)), demonstrating this a problem when trying to produce polymer at higher loadings. Relative integration of the $^{t}$Bu unit of catalyst **2** relative to the β-BL fragment confirms 1 methine proton ($H_A$) per phenyl ring ($H_B$), with both groups attached to the same phosphorus centre (Figure 6). All spectroscopic evidence supports assignment of this deactivated species, to be attached to the phosphorus centre in the deactivated species (**C**, Figure 6). The proposed structure for **C** is very similar to the known compound **D**, with a reported $^{31}$P chemical shift very close (14.9 ppm) to the deactivated species.[30]

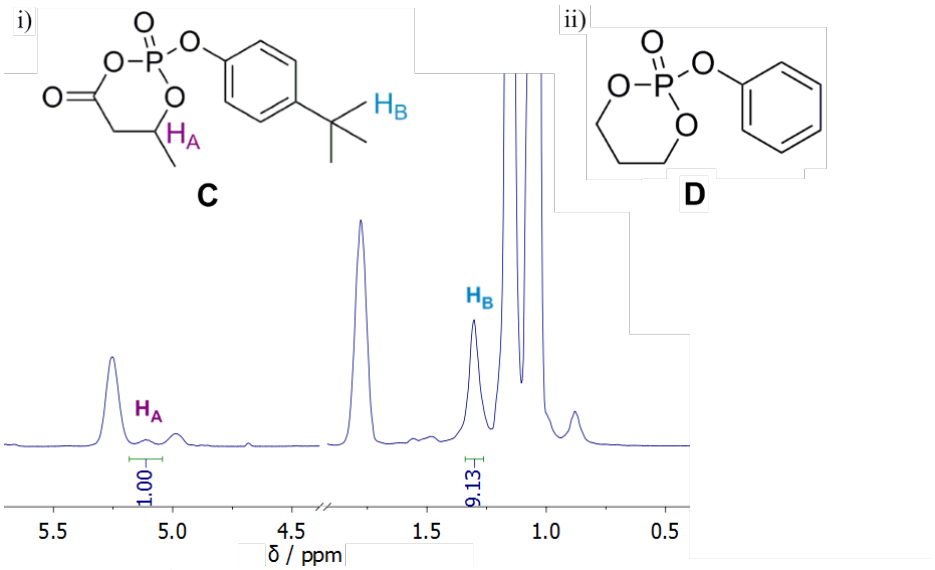
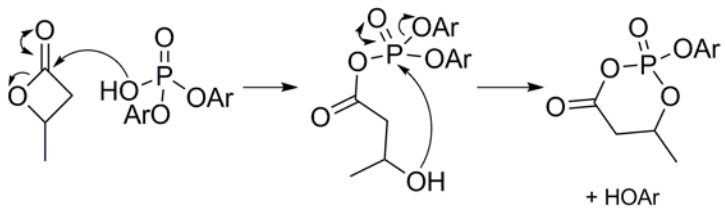



**Figure 6:** i) $^{1}$H NMR spectrum of polymerisation reaction mixture using catalyst **2**, with possible deactivated species structure ii) Structure of compound similar to deactivated species with similar $^{31}$P chemical shift.

A proposed decomposition pathway is shown in Scheme 3. Nucleophilic attack of the catalyst can open the β-BL monomer in an analogous reaction to the initiator free ROP (Table 2, Entry 1). Attack of the pendant alcohol on the phosphorus centre promotes elimination of one phenoxide fragment, chelating the central P atom. The labile P-O bond breaks without the aid of the initiator, as observed experimentally. This structure suggests why the β-BL monomer

presents such a unique challenge, as it forms a stable 6 membered ring structure when backbiting into the catalyst, as opposed to the 8 or 9 membered rings formed if lactide or caprolactone monomers decompose in similar ways.




**Scheme 3:** Proposed deactivation pathway of phosphoric acid catalysts with β-BL.

In the above pathway, it is the cleavable P-OR bond that facilitates decomposition. We hypothesised that replacing the P-OR bonds with stronger P-C bonds in phosphinic acid catalysts should block this deactivation pathway. As proof of concept a polymerisation of β-BL using diphenylphosphinic acid was tried, the activity of the catalyst was considerably lower, probably due to its lower acidity. However, no deactivated species was detected by NMR spectroscopy after 72 hours (Figure 7). The molecular weight also quintupled to 2000 Da compared to the parent diphenyl phosphoric acid and gave a dispersity of 1.23 (GPC trace in ESM).

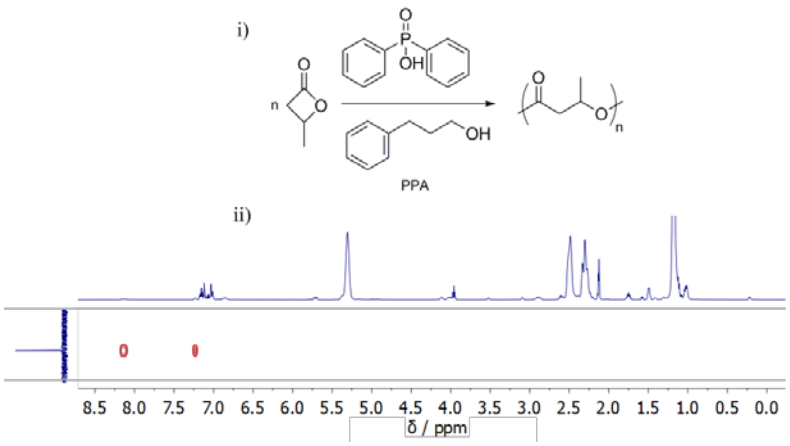


Figure 7: i) Reaction scheme using phosphinic acid ii) $^{31}P\{^{1}H\}$ NMR spectrum of reaction mixture after 3 days.

## 4. Conclusions

The unique challenge of ROP of β-BL by phosphoric acid organocatalysts has been explored through a combination of catalyst screening, kinetic studies, NMR characterisation and identification of decomposition products. Increased catalyst activity correlates with the electron deficiency and $pK_a$ of the phosphoric acid ligand. Through *in situ* NMR studies the formation of an off cycle product featuring chelation of a hydroxybutyrate fragment to form a 6-membered ring and elimination of a ligating phenoxide was discovered. The decomposition pathway can be prevented by replacing reactive P-OR bonds with P-Ph bonds. Understanding organocataylst mechanism and recognising the importance of unique monomer structure in catalyst performance will hopefully help to design new catalyst systems.

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