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# Polymerisation and stabilisation of polycaprolactone using a borontrifluoride–glycerol catalyst system

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**Abstract**

This paper describes a new synthetic route to poly-ε-caprolactone. A new cationic polymerisation has been developed which uses a borontrifluoride catalyst to open the caprolactone monomer, and glycerol to increase the molecular weights of the products. A post-treatment method has also been developed to reduce the amount of residual catalyst in the final product. This reduces the extent of borontrifluoride catalysed hydrolysis and therefore allows variation of the degradation rate of the material. 

*Keywords*: Caprolactone; Borontrifluoride; Degradation

## 1. Introduction

This paper describes a new polymerisation method developed to allow the easy production of degradable glass fibre composites for cranio- and maxillofacial bone repair. Polycaprolactone is a thermoplastic, having a very high melt viscosity (12 kPa s) [1], and is therefore not suitable for compression moulding about a fibre preform [2]. A monomer transfer moulding (MTM) method has been developed therefore in order to polymerise caprolactone monomer within the mould cavity about a fibre preform. This will ensure good impregnation of the fibre preform, a critical factor in obtaining optimum mechanical properties. This process is a variation on the resin transfer moulding (RTM) technique sometimes used in the manufacture of conventional composites [3].

Polycaprolactone has previously been investigated as a means of drug delivery [4] and it is known to be biocompatible and biodegradable. Cell culture techniques have been used to assess the biocompatibility of the material reported here; the results of these will be reported elsewhere.

Polycaprolactone is a biodegradable polyester which may be readily synthesised by cationic [5], anionic [6] and co-ordination polymerisation [7] as well as by free radical initiation [8]. Conventional co-ordination polymerisation of ε-caprolactone produces a high molecular weight straight-chain polymer with a narrow molecular weight distribution. It has a low $T_g$ of −80°C and a $T_m$ of 60°C, the polymer being around 57% crystalline at an $M_w$ of 120 kD[2]. However, free radical polymerisation of 1,3-dioxepane results in a branched polycaprolactone due to backbiting whereas cationic polymerisation of ε-caprolactone results in low molecular weight materials due to a competing equilibrium.

Conventionally, high molecular weight polycaprolactone is manufactured by co-ordination polymerisation using a tin [9] or aluminium alkoxide [10] catalyst. However, both tin and aluminium are toxic to humans and so a more acceptable catalyst system was sought. Initially, diethyl zinc with 1,4-butanediol [11] was tested. However, it was necessary to add the catalyst in either hexanes or toluene, both of which would remain in the end product and are not acceptable residues to remain in the final implant. Diethyl zinc is also very moisture- and air-sensitive and the rigorous conditions required for its handling resulted in complications in implementing the final manufacturing process.

This paper reports the use of a boron trifluoride catalyst for the cationic polymerisation of ε-caprolactone. It also describes the effects of adding glycerol as a termination agent in order to improve the molecular weight and physical properties of the polymer, and a post-treatment process using potassium fluoride which allows control over the catalytic degradation of the final product.

Boron trifluoride etherates are known to polymerise caprolactone, but the reversibility of the reaction gives rise to low molecular weight polymer ($M_w = 40$ kD),

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Table 1
The effect of variation of the borontrifluoride etherate concentration on the molecular weight of the polymer when glycerol is not used

| $BF_3{\cdot}OMe_2$ (M) | 0.051 | 0.029 | 0.026 | 0.021 | 0.017 |
|---|---|---|---|---|---|
| $M_w$ (Da) | 60 276 | 69 557 | 69 107 | 66 681 | 70 398 |
| $M_n$ (Da) | 33 520 | 40 238 | 43 101 | 42 005 | 43 130 |

which in turn results in poor mechanical properties. The final properties of the polymer further deteriorate as the residual borontrifluoride catalyst catalyses the hydrolysis of the polymer. It is for this reason that boron trifluoride is conventionally employed for the production of co-polymers with phenyl glycidylether [12] or 3,3-bis(chloromethyl) oxetane [13] rather than for the synthesis of the polycaprolactone homopolymer. In order to circumvent the problem of low molecular weights and reduce the effects of any water contamination, glycerol was added. This results in the formation of branched polymers which have much higher molecular weights than those produced in reactions without glycerol. This use of glycerol in the polymerisation of caprolactone is not new and has already been reported in the literature [10].

The structural integrity and dimensional stability of the composite are vital features in the production of patient-specific implants ruling out a solvent extraction. It is therefore difficult to remove the borontrifluoride catalyst from the polymer. The borontrifluoride residue catalyses the hydrolysis of the polymer resulting in an increased degradation rate for the material, causing its properties to deteriorate rapidly. In cell culture experiments with osteoblast bone cells, the leaching of acidic toxins into the cell culture medium during degradation kills the cells. This degradation problem has been overcome by using a post-treatment with fluoride ions which react with the catalyst residues and reduce the activity of the boron catalyst without affecting the integrity of the composite.

## 2. Experimental

The final implants are expected, on average, to have volumes of approximately 2 $cm^3$ and the moulds will be machined from poly(tetrafluoroethene) (PTFE). Therefore, in order to find a model for the chemistry to aid future production of the composite in a manufacturing environment, several PTFE reaction vessels were manufactured. These consisted of 30 PTFE tubes sealed at one end and fitted with stoppers. The volume of the tubes was ~2.5 $cm^3$, similar to that of possible moulds.

Caprolactone monomer (Solvay Interox) was distilled under reduced pressure from calcium hydride and was further treated by bubbling nitrogen through to remove dissolved oxygen. A 1 M solution of glycerol in caprolactone was then prepared by dissolving 730 μl of glycerol (Aldrich HPLC grade, used as received) in 10 ml of dry caprolactone monomer. The PTFE reaction tubes were dried under vacuum at 140°C for 12 h. Each tube was then charged with the required amount of caprolactone monomer and glycerol solution to make a total volume of 2 ml. The reaction mixture was treated with the required amount of boron trifluoride dimethyletherate (Aldrich, used as received) and agitated. The tubes were heated in an oven at 80°C for 32 h. At the end of the reaction samples were removed from the tubes and the molecular weight analysed by gel permeation chromatography (GPC) (Polymer Labs, mixed D columns, 35°C 1 ml $min^{-1}$ against PS-1 polystyrene narrow standards).

Further samples for studying the polymer degradation were prepared using a flat plate mould manufactured from PTFE. This has a rectangular cavity (80 mm × 30 mm × 2 mm) and will be used in future experiments to study the properties of the composite. In cases where the flat plate mould was used, the caprolactone monomer was prepared in the same manner as described previously. The moulds, fittings, tubing and syringe were all dried in a vacuum oven at 140°C overnight. Glycerol (129 μl) was then added to 60 ml of caprolactone and 159 μl boron trifluoride dimethyletherate added. The reaction is sufficiently slow at room temperature to allow the slow injection into the mould. It was then sealed and heated in an oven for 32 h at 80°C. At the end of the reaction the mould was allowed to cool and the plate removed.

In cases where the post-treatment process was assessed, a polycaprolactone plate was cut into strips of approximately 2 mm width and soaked in a saturated solution of potassium fluoride (Aldrich 99 + %, used as received) in ethanol (Aldrich HPLC grade). The strips were then allowed to degrade in air and their molecular weights measured at regular intervals by GPC.

## 3. Results and discussion

### 3.1. Polymer synthesis

The molecular weight data for the assessment of the $BF_3{\cdot}OMe_2$–glycerol system gave bi- and multi-modal distributions (PDI 3.5–4), as is expected for reactions where there are a large number of possible structures for the polymer. Reactions which did not include glycerol showed little variation in molecular weight (either $M_w$ or $M_n$) with increasing catalyst concentration (Table 1) with the exception of reactions where the boron catalyst is at very high concentrations. This fits well with previously obtained results [14] and theories which describe the cationic polymerisation of caprolactone as a living system where there is an equilibrium between chain extension and chain degradation reactions.

The cationic polymerisation reactions were also conducted using a small amount of glycerol at a range of concentrations. The glycerol provides a species with which

Table 2
The effect of various concentrations of glycerol on the molecular weight of polycaprolactone during the borontrifluoride dimethyl etherate catalysed polymerisation of caprolactone

| Concentration of glycerol (M) | Concentration of $BF_3{\cdot}OMe_2$ (M) | | | | |
|---|---|---|---|---|---|
| | 0.051 | 0.029 | 0.026 | 0.021 | 0.017 |
| Values of $M_w$ for the polymerisation (Da) | | | | | |
| 0.051 | 105 968 | 118 482 | 106 343 | 100 686 | 126 838 |
| 0.029 | 83 934 | 92 113 | 86 667 | 95 403 | 10 6363 |
| 0.026 | 85 155 | 96 257 | 85 758 | 98 124 | 92 871 |
| 0.021 | 80 637 | 88 578 | 77 203 | 81 168 | 93 984 |
| 0.017 | 71 571 | 82 863 | 72 288 | 72 256 | 78 937 |
| Values of $M_n$ for the polymerisation (Da) | | | | | |
| 0.051 | 25 027 | 29 246 | 33 816 | 28 778 | 27 452 |
| 0.029 | 28 147 | 25 970 | 27 469 | 26 031 | 27 671 |
| 0.026 | 29 644 | 31 681 | 28 179 | 30 352 | 30 181 |
| 0.021 | 33 049 | 33 834 | 28 069 | 32 112 | 34 561 |
| 0.017 | 28 973 | 33 960 | 28 403 | 28 950 | 31 942 |

growing polymer chains can terminate, but which has further hydroxyl groups available for chain extension. This resulted in a broadening of the molecular weights and a large increase in the values for $M_w$. However, the values for $M_n$ remained fairly constant (Table 2). In the best cases the values for $M_w$ are almost double those found for reactions where glycerol is not used. These reactions produce a polymer with a broad molecular weight distribution, therefore a large amount of the polymer is of a molecular weight higher than the chain entanglement length (>50 000 D). The resulting polymer therefore has good physical properties, its Young's modulus being

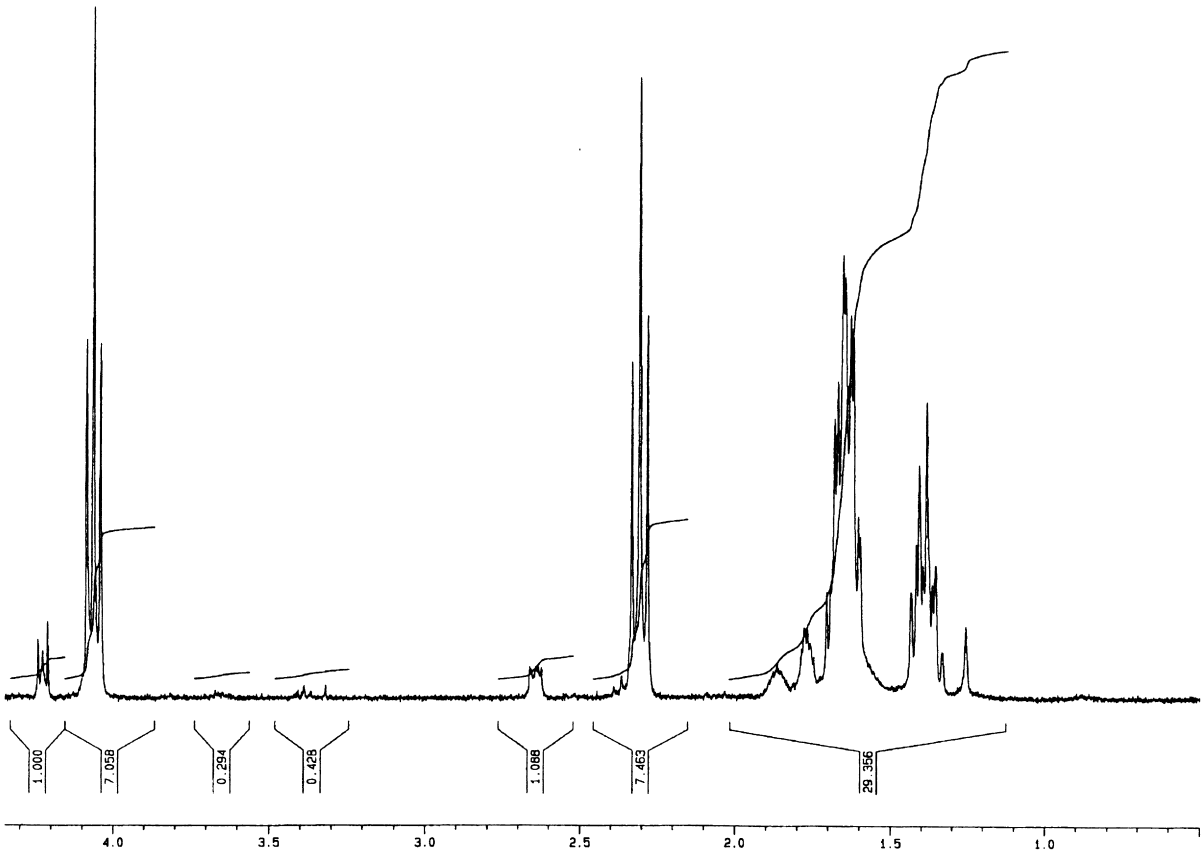


Fig. 1. $^1$H NMR of the polymer. Polymer bands at $CH_2$– 1.4 and 1.7 ppm, $CH_2C{=}O$ 2.3 ppm, $CH_2$–O 4.25 ppm, glycerol CH at 3.3–3.5 ppm, trace dimer at 2.65 and 4.5 ppm.

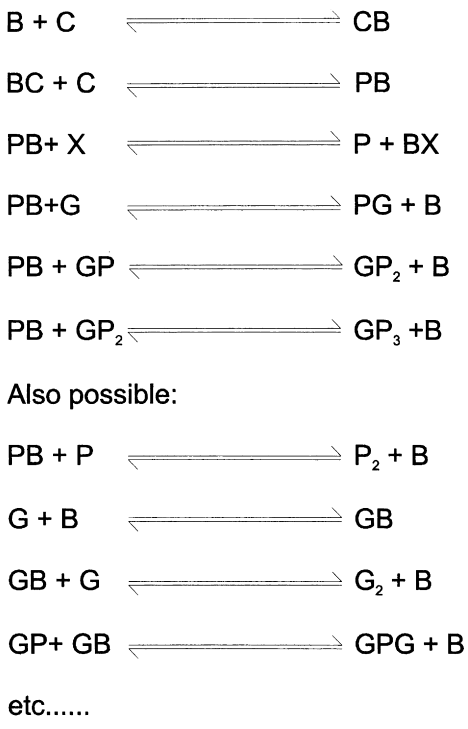


Fig. 2. Equations describing the kinetics of the polymerisation (C = caprolactone monomer, B = boron catalyst, P = caprolactone polymer, G = Glycerol, X = impurity ($H_2O$, alcohol, etc.)). The molecular weight of the polymer will depend heavily on the state of equilibrium of several inter-related reactions.

400 MPa. Commercial material such as Capa 680, (Solvay Interox; $M_w = 120$ kD), typically has a Young's modulus of 440 MPa. The material was found to dissolve slowly in chloroform showing that the material is not cross-linked. The $T_m$ and $T_g$ of the material were also measured by differential scanning calorimetry (DSC; −100 to 90°C; scan rate 20°C $min^{-1}$) using a Perkin Elmer DS7. The $T_m$ was found to be 55°C and the degree of crystallinity 59% compared to pure polycaprolactone. The $T_g$ could not be detected even at scan rates as low as 0.5°C $min^{-1}$. $^1$H NMR (Fig. 1) analysis showed a spectrum similar to that for pure polycaprolactone ($CH_2$ 1.4 and 1.7 ppm, $CH_2C{=}O$ 2.3 ppm, $CH_2{-}O$ 4.5 ppm). There were peaks at 2.65 and 4.25 ppm due to cyclic dimer and peaks at 3.3–3.5 ppm due to the glycerol groups.

An analysis of the effects of the concentration of borontrifluoride and glycerol on the molecular weight was undertaken in order to formulate an empirical model for $M_w$ for this polymerisation. Initially, the fitting of reaction kinetics to the data was considered. The kinetics of the reaction must take into account several inter-related reactions (Fig. 2). Both propagation and termination reactions affect the molecular weight in different ways and in some cases the concentration of both glycerol and caprolactone varies with the rate of propagation or termination. A detailed kinetic study therefore was considered too complex at this time.

A further problem with assessing the kinetics is the uncertainty surrounding the molecular configuration of the polymer. Owing to the high molecular weight of the polymer it is not easy to assess quantitatively the proportion of glycerol units in each chain. It is therefore not possible to determine if the glycerol acts purely as a terminating agent or as a comonomer by becoming a repeat unit in the polymer itself. $BF_3$ is known to catalyse transesterification reactions, hence a completed polycaprolactone chain could form an ester link with a glycerol unit or with another hydroxyl terminated PCL fragment. $^1$H NMR spectra of pure glycerol show broad bands for the OH and CH groups but the CH bands of the glycerol in the polymer are sharp (Fig. 1), therefore small shifts in these bands cannot be resolved. Considerably more study would be required to answer the question of how the glycerol is distributed along the polymer chain. By contrast, this study focuses on the production of biocompatible materials with good degradation and mechanical properties.

In order to obtain an empirical model of how the reagent concentrations affects the molecular weight, experiments were conducted with $BF_3{\cdot}OMe_2$ at concentrations from 0.0169 to 0.051 M and the glycerol concentration varied from 0 to 0.051 M. A $^1$H NMR was recorded of a sample (Fig. 1), this proved very similar to that of the commercial material. The peaks at 2.65 and 4.25 ppm are the cyclic dimer. The molecular weights for each of the samples were also measured and used to plot graphs of the ratio of $BF_3{\cdot}OMe_2$ to glycerol concentration at various concentrations of $BF_3{.}OMe_2$ (Table 3). The data in these graphs were then used to fit Eq. (1).

$$\text{Molecular weight} = \frac{A}{\text{Ratio}} + B \quad (1)$$

The resulting coefficients are recorded in Table 4. In order to produce a base line data point the ratio of $BF_3$ to glycerol

Table 3
The variation of $M_w$ at various $BF_3{\cdot}OMe_2$ concentrations with the ratio of the concentration of $BF_3{\cdot}OMe_2$ to that of glycerol

| $BF_3 = 0.051$ | | $BF_3 = 0.029$ | | $BF_3 = 0.026$ | | $BF_3 = 0.021$ | | $BF_3 = 0.017$ | |
|---|---|---|---|---|---|---|---|---|---|
| Ratio B:G | $M_w$ | Ratio B:G | $M_w$ | Ratio B:G | $M_w$ | Ratio B:G | $M_w$ | Ratio B:G | $M_w$ |
| 1.00 | 105 968 | 0.57 | 118 482 | 0.50 | 106 343 | 0.40 | 100 686 | 0.33 | 126 838 |
| 1.77 | 83 934 | 1.00 | 92 113 | 0.89 | 86 667 | 0.72 | 95 403 | 0.58 | 106 363 |
| 2.00 | 85 155 | 1.13 | 96 257 | 1.00 | 85 758 | 0.81 | 98 124 | 0.66 | 92 871 |
| 2.47 | 80 637 | 1.40 | 88 578 | 1.24 | 77 203 | 1.00 | 81 168 | 0.82 | 93 984 |
| 3.03 | 71 571 | 1.71 | 82 863 | 1.52 | 72 288 | 1.23 | 72 256 | 1.00 | 78 937 |

Table 4
A table of coefficients found by fitting Eq. (1) to the data in Table 4, errors shown in brackets. This data gives two straight-line fits for $A$ and $B$ with respect to the concentration of $BF_3{\cdot}OMe_2$ $A = 913\,240x - 300$; $r^2 = 0.957$ and $B = -252\,280x + 72\,460$; $r^2 = 0.871$

| Concentration of $BF_3{\cdot}Ome_2$ | Coefficient ($A$) | Coefficient ($B$) |
|---|---|---|
| 0.051 | 47 000 (3000) | 59 000 (2000) |
| 0.029 | 28 000 (2000) | 68 000 (2000) |
| 0.026 | 20 000 (3000) | 64 000 (3000) |
| 0.021 | 15 000 (4000) | 68 000 (6000) |
| 0.017 | 20 000 (3000) | 67 000 (4000) |

at zero glycerol (i.e. ratio = ∞) was taken to have a value of 100, this point being far in excess of the other ratio values. The data for the fitted equations were then plotted against the appropriate concentration of $BF_3{\cdot}OMe_2$ (Table 4). This gave two straight-line plots for the coefficients $A$ and $B$ from Eq. (1).

It was therefore possible to relate the two linear equations for the coefficients in Eq. (1) to give a single equation (Eq. (2)) which describes the variation of $M_w$ with varying glycol and $BF_3{\cdot}OMe_2$ concentration.

$$\text{Molecular weight, } M_w = \frac{913\,240[BF_3][G] - 300[G]}{[BF_3]} - 252\,280[BF_3] + 72\,460 \qquad (2)$$

(G = glycerol, $BF_3 = BF_3{\cdot}OMe_2$).

The estimated values for $M_w$ found using this equation, and the experimental values found previously were compared and found to be in good agreement (Table 5) especially at high concentrations of $BF_3{\cdot}OMe_2$. It is thought that the larger effect of water on the reaction at low $BF_3{\cdot}OMe_2$ concentrations is responsible for the deviation in molecular weight.

### 3.2. Polymer degradation study

Despite the inclusion of glycerol in the polymer, the residual $BF_3{\cdot}OMe_2$ catalyst also catalyses the degradation of the polymer, even in air. In water, this degradation results in a drop in molecular weight of approximately 50% in 24 h. In an attempt to control this degradation, the polymer was soaked in a saturated solution of potassium fluoride in ethanol. This would allow the potassium fluoride to penetrate the polymer and result in the formation of potassium tetrafluoroborate. The tetrafluoroborate salt would not further catalyse the hydrolysis of the polymer and therefore the $BF_3{\cdot}OMe_2$ catalyst would be removed from the system. The use of this procedure was not found to adversely affect cell growth and biocompatibility as will be reported elsewhere.

Table 5
A comparison between the experimental and estimated results for various concentrations of $BF_3$ and glycerol. This shows little deviation of the model from experimental results. The model is especially accurate at high $BF_3{\cdot}OMe_2$ concentrations

| Conc. $BF_3$ (M) | Conc. glycerol (M) | $M_w$ exp. | $M_w$ est. | % Deviation |
|---|---|---|---|---|
| 0.051 | 0.051 | 105 968 | 105 868 | 0.1 |
| 0.017 | 0.017 | 789 937 | 83 396 | 5.0 |
| 0.051 | 0.017 | 71 571 | 75 019 | 4.6 |
| 0.017 | 0.051 | 126 838 | 113 846 | 11.4 |

Table 6
The effect of an 11-h treatment of the polymer contaminated with $BF_3{\cdot}OMe_2$ in a potassium fluoride in ethanol bath on the degradation of the polymer in air

| Degradation time (h) | Untreated polymer ($M_w$ kD) | Treated polymer ($M_w$ kD) |
|---|---|---|
| 0 | 125 | 121 |
| 18 | – | 109.8 |
| 29.5 | 91.7 | – |
| 36.5 | – | 109.8 |
| 47.5 | 86.8 | – |
| 60.5 | – | 115.5 |
| 72.5 | 78.2 | – |
| 79.5 | – | 114.7 |
| 92 | 72.7 | – |

A polymer plate was cut into several strips (2 mm × 2 mm × 30 mm) and the strips soaked in the potassium fluoride solution for 11 h. The molecular weight of the polymer was recorded at regular intervals as the polymer degraded (Table 6). It was found that after only 11 h of treatment, the degradation of the polymer had been slowed significantly. This resulted in a material which retained its mechanical properties for long periods after treatment, had good biocompatibility and a variable degradation rate.

## 4. Conclusions

It has been shown that borontrifluoride dimethyl etherate may be used as a catalyst for the polymerisation of caprolactone. It has also been shown that the molecular weight and hence the mechanical properties of the polymer can be improved greatly by the addition of glycerol to the reaction mixture in order to increase the molecular weight of the polymer. It has been shown that fluoride ions may be used to retard and control the $BF_3{\cdot}OMe_2$ catalysed degradation of the polymer. Future work will study the role of the solvent for the post-treatment and further test the effect of temperature on the polymerisation reaction.

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