CHAPTER 4

CONCLUSIONS

From the results of this project, as presented and discussed in Chapters 2 and 3, the following conclusions can be drawn regarding the kinetics of the polycondensation of glycolic acid in bulk and the synthesis of higher molecular weight poly(glycolic acid).

4.1 Kinetics of Polycondensation of Glycolic Acid

The kinetics of polycondensation of glycolic acid have been studied in this project through a series of 9 experiments conducted under various pre-designed conditions :

(A) Uncatalysed Polyesterification

RUN 1 : at 150°C under an atmospheric pressure of N_2
RUN 2 : at 150°C/atm/N_2 followed by at 180°C/reduced pressure
RUN 3 : at 150°C/atm/N_2 followed by at 200°C/reduced pressure

(B) p-Toluenesulfonic Acid-Catalysed Polyesterification

Except for the addition of p-toluenesulfonic acid as catalyst, the conditions used for RUNS 4-6 were the same as for the previous uncatalysed RUNS 1-3 listed above.

(C) Antimony Trioxide-Catalysed Polyesterification

Except for the addition of antimony trioxide as catalyst, the conditions for RUNS 7-9 also corresponded to those previously given for RUNS 1-3 respectively.

According to the kinetic theory of condensation polymerisation, a catalysed polyesterification reaction should obey second-order kinetics and an uncatalysed reaction should obey third-order kinetics. The corresponding rate equations are :

$$\text{CATALYSED} \qquad 1/(1-p) = 1 + k_2\,[\mathrm{COOH}]_o t$$

$$\text{UNCATALYSED} \qquad 1/(1-p)^2 = 1 + 2k_3\,[\mathrm{COOH}]_o{}^2 t$$

where k_2 and k_3 are the second-order and third-order rate constants respectively.

The results for RUNS 1-9 are summarized for ease of comparison in Table 4.1.

Table 4.1 : Comparison of kinetic parameters for glycolic acid polyesterification experiments.

RUN	Conditions	p_{max}	p range of slope	Second-order Rate Constant, k_2 g/equiv-min	Third-order Rate Constant, $k_3 \times 10^{-2}$ $(g/equiv)^2 min^{-1}$
1	150 °C/atm./N_2	0.884	0.725-0.847	–	17.5
			0.853-0.884	–	3.5
2*	180 °C/red.press.	0.954	0.859-0.946	–	89.7
			0.944-0.948	–	8.4
3*	200 °C/red.press.	0.976	0.865-0.955	–	97.0
			0.957-0.976	–	145.7
4	150 °C/atm./N_2	0.974	0.917-0.960	26.0	–
5*	180 °C/red.press.	0.977	0.928-0.968	28.2	–
6*	200 °C/red.press.	0.979	0.947-0.976	29.0	–
7	150 °C/atm./N_2	0.909	0.901-0.903	4.3	–
8*	180 °C/red.press.	0.926	0.863-0.926	8.4	–
9*	200 °C/red.press.	0.962	0.913-0.919	9.2	–

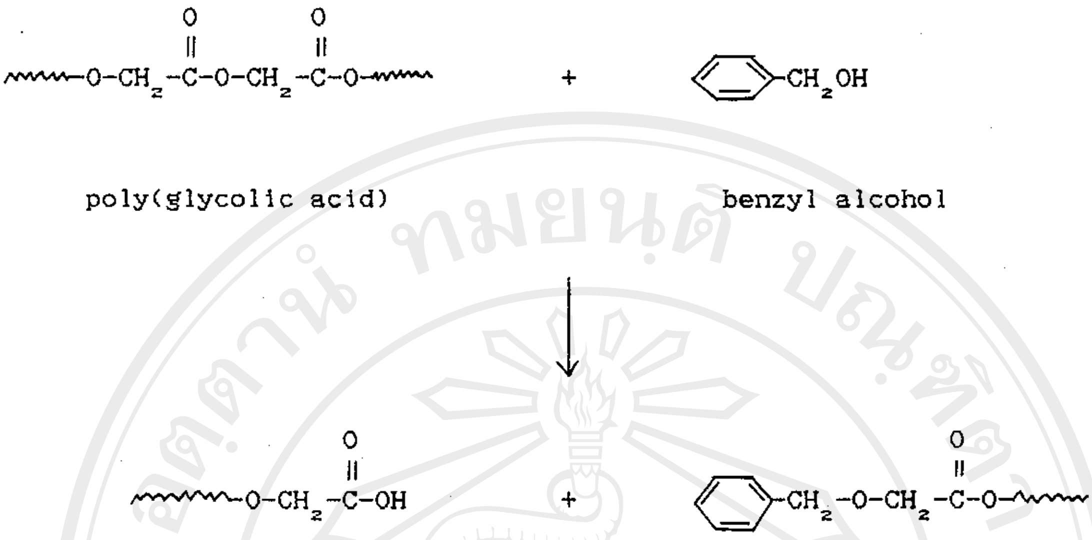
* after solidification at 150 °C/atm/N_2

From the kinetic studies, it can be concluded that self-catalysed polyesterification occurs at a relatively slow rate and gives only low molecular weight polymer. Using a catalyst leads to increases in both reaction rate and final molecular weight. Comparing the two catalysts used in this work, p-toluenesulfonic acid was the more effective, probably because it was homogeneous with the monomer melt whereas antimony trioxide was heterogeneous.

However, as the kinetic plots in Chapter 2 showed, adherence to the theory is rather limited in practice. The relevant plots in Figs. 2.2, 2.4, 2.6, 2.9-2.14 were approximately linear against time only over limited ranges of conversion. These observed deviations from the theory have been attributed to various effects, notably the changing dielectric of the system as it changes from an acid-alcohol medium to an ester product. In addition, other effects arising from the method of kinetic analysis should also be considered, for example :

(a) Possibility of Alcoholysis in Hot Benzyl Alcohol

In these experiments, a modified hot titration technique was used employing benzyl alcohol as solvent. It is conceivable that the ester groups in the polymer's main chain could undergo alcoholysis by the benzyl alcohol solvent at high temperature during dissolution. This possibility may be represented by the following equation :



Degradation of poly- -esters in hot benzyl alcohol was studied by COOH end-group analysis and found to increase with time of dissolution [15]. This was attributed to the occurrence of some chain scission in the polymer leading to an increase in [COOH] up to a limiting value. This view was supported in a more recent study [71] in which it was observed that the COOH end-group concentration in PGA in hot benzyl alcohol solution increased slightly as the polymer dissolved and then reached a constant level. However, this increase in [COOH] was considered to be relatively small compared with the base value at complete dissolution and also occurred only very slowly over a long period of time (0.04-0.05 x 10^{-3} g-equiv for t 55-200 mins). Consequently, it would be expected that this reverse alcoholysis reaction would have a very slow rate. Since, in this work, the time of dissolution of the polymer products was about 10-60 mins, this effect should have relatively little influence on the final titration results.

In addition, this alcoholysis reaction may be catalysed by the polymer's own COOH chain-end groups with the sodium hydroxide titrant also acting as a saponification catalyst at elevated temperatures (> 100 °C). However, this latter possibility was avoided in the modified cooled (< 50 °C) titration method employed in this work since the temperature of the titration was not high enough for saponification to occur. In this method, chloroform was used as a liquefier and dispersant to keep the PGA in metastable solution at a reduced temperature at which it would normally precipitate from benzyl alcohol alone [15, 34].

(b) Effects of Other Factors

The various sources of error in the experiments which may have also contributed to the kinetic irregularities include, for example :

(i) Temperature variations of up to ± 5 °C, the limits to which the reaction temperature could be controlled, can have a significant effect on the results obtained in a kinetic experiment.

(ii) In the COOH end-group titrations using a modification of Pohl's method [34], the titrimetric precision was checked and found to be of the order of ± 5%.

Turning our attention now to the effects of the various reaction variables, the following conclusions can be drawn :

(1) Effect of Temperature

All of the results for each system given in Table 4.1 show that, as the reaction temperature is increased, the rate of reaction also increases. This is in accordance with the well-known Arrhenius Equation [72] :

$$k = A \exp(-E/RT)$$

where

k = rate constant
A = frequency factor
E = activation energy
R = universal gas constant
T = reaction temperature

(2) Effect of Catalyst

Although the respective rate constants k_2 and k_3 for the catalysed and uncatalysed reactions cannot be compared directly because of their different orders, it can be seen from the kinetic profiles that the rate of the uncatalysed reaction is very much slower than the catalysed reactions, especially when the catalyst is p-toluenesulfonic acid. This is because, in the absence of added catalyst, the COOH groups must act as the acid catalyst themselves. However, because the COOH groups are also reactants, their catalytic effect declines with their concentration as the reaction proceeds. The uncatalysed reaction therefore requires much longer reaction times before the maximum level of conversion is reached.

(3) Effect of Pressure

When a vacuum pump is connected to the system in order to reduce the pressure, a higher rate of reaction, higher conversion, and higher molecular weight of the polymer product is obtained. This is because, at the reduced pressure, the continuous removal of the water by-product can be more efficiently achieved, thus driving the reaction equilibrium more towards polymer formation.

4.2 Synthesis of Glycolide

The synthesis of glycolide is a two-step synthesis involving, firstly, the linear polycondensation of glycolic acid to low molecular weight PGA followed, secondly, by thermal decomposition of the PGA to yield glycolide as the primary decomposition product. In this work, the experimental conditions used for the 1st step were based on the previous kinetic studies. Three experiments were designed.

RUN 1	1st Step 2nd Step	Uncatalysed Sb_2O_3-catalysed
RUN 2	1st Step 2nd Step	PTSA-catalysed Sb_2O_3-catalysed
RUN 3	1st Step 2nd Step *	Sb_2O_3-catalysed Sb_2O_3-catalysed

* without further addition of Sb_2O_3

From the results previously shown in Table 3.1/page 99, it was considered that the conditions used in RUN 3 gave the best results for the synthesis of glycolide from the point of view of yield, appearance, melting range and practical convenience. Pure glycolide was obtained as a white crystalline solid of melting range 82-84 °C. Precautions which needed to be taken in the handling of glycolide in order to ensure the best results for subsequent polymerisation were :

(a) the crude glycolide was recrystallized immediately after synthesis ;

(b) during the recrystallisation procedure, the glycolide was protected from atmospheric moisture as much as possible by passage of dry nitrogen gas during dissolution and by filtering the recrystallized glycolide in a controlled nitrogen atmosphere glove box ;

(c) the recrystallized glycolide was stored in a vacuum desiccator for a period not exceeding 1 week before it was used for polymerisation.

The pure glycolide product from RUN 3 was of melting range 82-84 °C and was obtained in 68.7% yield based on the initial glycolic acid (cf., lit. [32] : m.p. 82-84 °C, 26.7% yield). Also, its V'ant Hoff purity was determined by DSC in another research project carried out concurrently with this one [73] and was found to be 99.14% (cf., commercial glycolide : 99.26%). The DSC curves used for those purity analyses are shown in Fig. 4.1.

A general conclusion which can be drawn from the results obtained in this work is that the synthesis of glycolide is not easy. It requires practical experience in order to be able to manipulate the conditions, particularly the temperature during Step 2, so as to optimize the yield and purity of the glycolide product. Furthermore, the purity of the glycolide, as evidenced by its appearance and melting range, seems to have an important influence on its subsequent polymerisability. The higher its purity and the sooner it is used after synthesis, the more easily it seems to polymerise. This could be related to the reported existence of two polymorphic forms of glycolide, an α-form and a β-form, one of which (the β-form) exhibited erratic polymerisation behaviour unless it was used shortly after its preparation [31].

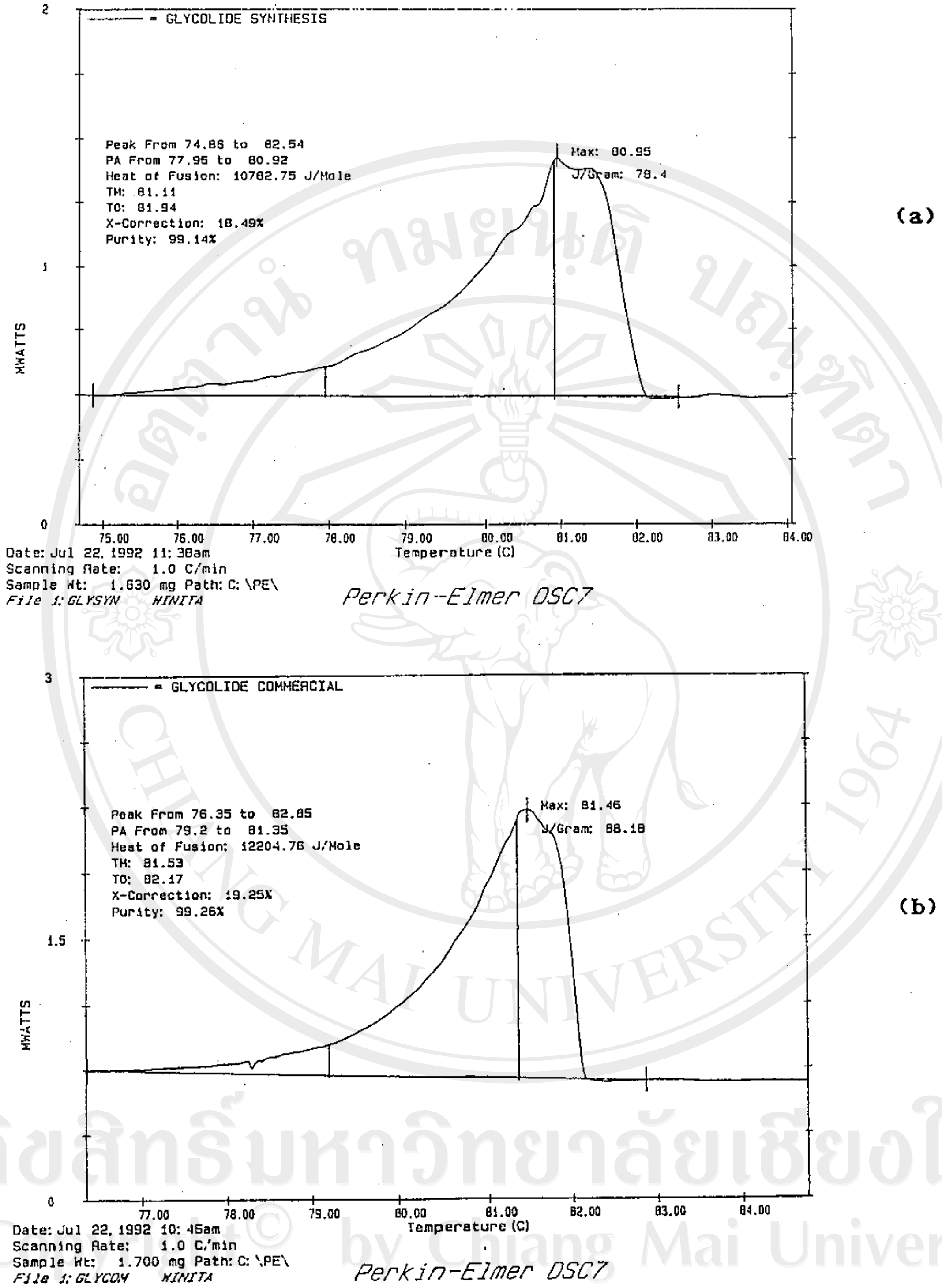


Fig. 4.1 : DSC curves showing the results of purity analysis [73] :

(a) recrystallized glycolide product (from RUN 3);

(b) commercial glycolide sample (Polysciences, Inc.).

Table 4.2 : **Glycolide polymorphs (taken from [31]).**

Physical Property	α -form	β -form
Stability range	42 - 82-85 °C (m.p)	Below 42 °C
Crystal system	Orthorhombic	Monoclinic
Refractive index		
n_α	1.486	1.430
n_β	1.506	1.555
n_γ	1.620	1.568
Vapour pressure, mm at 20 °C	0.04	0.02

Another notable feature of the results is that it does not appear that the molecular weight of the intermediate low molecular weight PGA from Step 1 has any significant effect on the eventual yield of glycolide from Step 2. It was originally thought that, because of the way in which the PGA chain has to fold back on itself in order to eliminate glycolide via an intramolecular ester interchange mechanism (see Scheme 3.1 on page 105), the initial chain length may have an effect on the ease with which this process can take place. However, there is no conclusive evidence for this. Instead, it must be concluded that the differences in the results of glycolide synthesis shown in Table 3.1/ page 99, are more likely to be due mainly to variations in :

(1) efficiency of reaction control (especially temperature and pressure) during glycolide distillation ;

(2) efficiency of the recrystallisation procedure, particularly with respect to safeguarding the glycolide against hydrolysis by contact with atmospheric moisture ; and

(3) possible different extents of polymorphism in the crude products resulting from differences in the reaction conditions.

4.3 Synthesis of Higher Molecular Weight PGA

Higher molecular weight PGA has been obtained from the ring-opening bulk polymerisation of glycolide using various reaction conditions. These conditions can be summarized as follows :

Initiators : aluminium triethyl
antimony trifluoride
stannous octoate
stannous oxalate
Reaction temperatures : 180 °C, 200 °C, 220 °C
Reaction times : 10 mins., 30 mins., 1-7 hours
Pressure : atm. press. of N_2 gas

From the results obtained, the effects of the reaction variables studied in these experiments have been discussed and the following conclusions drawn.

(1) Effect of Reaction Time

At a given polymerisation temperature, the melting characteristics of polymer samples, as determined analytically by DSC, showed little change in terms of the position and shape of the melting peak with increasing time after solidification. The slight changes that did occur can be attributed to a gradual narrowing of the size distribution of the crystalline regions in the solid state with time by the process of annealing. Annealing at temperatures between a polymer's crystallisation temperature (T_c) and melting point (T_m) is well known to be able to bring about gradual increases in both molecular weight and crystallinity in linear polyester condensates [35]. However, this aspect of solid-state behaviour is less well documented for ring-opening polyesters formed via an addition-type mechanism. Also, annealing for molecular weight and morphology enhancement purposes is usually carried out over much longer times and lower pressures than those employed (7 hours at atm. press.) in this work.

(2) Effect of Reaction Temperature

The effect of increasing the polymerisation temperature from 180 °C to 200 °C was to increase and narrow the polymer melting range (from DSC). However, at 220 °C, thermal degradation occurred. Clearly, an optimum temperature exists at which molecular weight and morphology development can be maximized without accompanying thermal degradation. However, this situation is complicated by the fact that higher molecular weight PGA, with its higher melting point ($T_m \approx 220\,^{\circ}C$), is thermally unstable in the melt. The major consequence of this is that the polymer has a very narrow "processing window". This necessitates very strict temperature control during both synthesis and melt spinning, operations which, in industry, are therefore carried out as a continuous process.

(3) Effect of Initiator

Under the same reaction conditions (temperature, time, initiator concentration, etc.), the different initiators produced slightly different results. For example, the physical appearances, melting ranges and intrinsic viscosities of the polymer products varied slightly, presumably due to the different initiator efficiencies. This, in turn, is related to the mechanism by which each initiator acts and their respective reactivities towards the glycolide ring. Also, it should be mentioned that, in this work, the chosen initiator concentration of 1% by mole proved to be rather high and produced fast reactions but relatively low molecular weights in all cases. A lower concentration of, say, 0.1% by mole might be used in future work.

(4) Effect of Purification

Finally, it is also worthy of mention here that purification of the crude polymer product by reprecipitation from solution in hot DMSO as solvent had the opposite effect to that intended. It was found that the DMSO solvent used to dissolve the PGA remained in contact with the polymer after purification as a contaminant. This residual solvent both lowered and broadened the polymer melting range relative to that of the crude product. The inference from this is that, if possible, purification by dissolution and reprecipitation should be avoided. Instead, the synthesis conditions should be improved in order to maximize the % conversion and, hence, the purity of the crude product followed, if necessary, by hot alcohol (absolute) extraction to remove any residual monomer and/or oligomer impurities.

In conclusion, the structural conversions in the sequence of products obtained : low molecular weight PGA, glycolide, and higher molecular weight PGA, can be demonstrated quite clearly by IR spectroscopy, as shown in Figure 4.2. This Figure, in effect, summarizes the changes which have been discussed in detail in the previous two chapters.

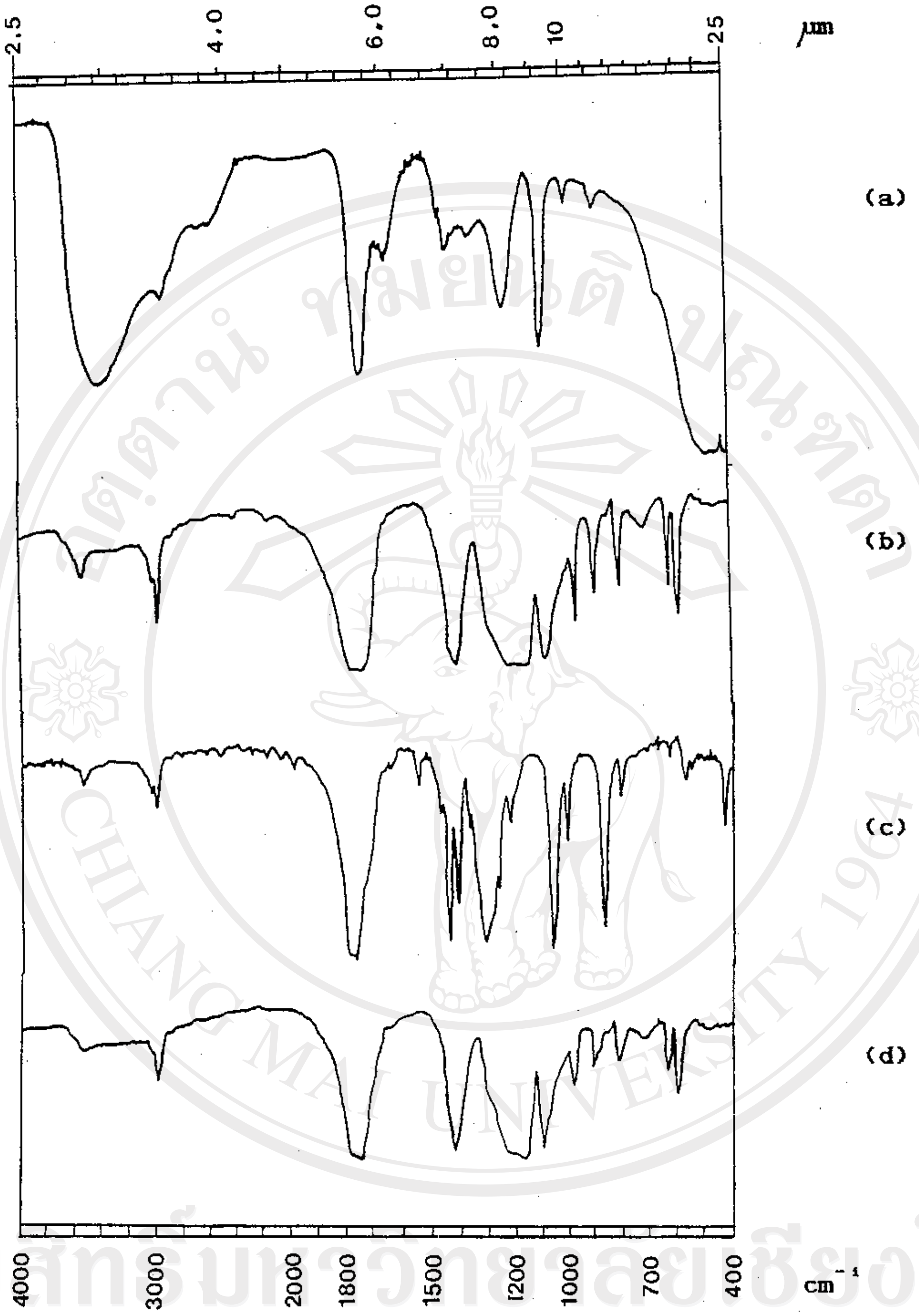


Fig. 4.2 : Comparison of infrared spectra showing the sequence of structural changes in the synthesis of PGA :

(a) glycolic acid (starting material);

(b) low molecular weight PGA;

(c) glycolide;

(d) higher molecular weight PGA (crude).

SUGGESTIONS FOR FURTHER WORK

As an extension of the work described in this thesis, the following suggestions for further study are proposed.

1. In order to increase both the yield and purity of the final glycolide product used for polymerisation, the recrystallisation procedure for the crude glycolide should be further refined. It is possible, for example, that for complete recrystallisation to take place from ethyl acetate, much longer times at lower temperatures than those used in this work may be required.

2. For the bulk polymerisation of glycolide, an initiator concentration of 1% by mole was employed throughout. This should be reduced in order to increase the molecular weight of the polymer up to, at least, a level which would be suitable for melt spinning ($\overline{M}_n$ > 20,000).

3. In the case of the aluminium triethyl initiator, its efficiency could be improved by reacting it with precisely known amounts of water as coinitiator. The $Al(C_2H_5)_3 : H_2O$ ratio is reported to have an effect on the yield and molecular weight of the polymer formed and it would be very useful to know the optimum ratio for glycolide polymerisation.

4. For polymers such as poly(glycolic acid) (PGA) that are used in biomedical applications, it is essential that they are prepared in as high a state of chemical purity as possible. Contact with organic solvents should be minimized and so purification by dissolution and reprecipitation should be avoided. Ways therefore need to be found of maximizing the % conversion of the glycolide monomer in bulk so that the PGA product is as pure as possible. If necessary, any remaining impurities (e.g., residual monomer, initiator residues, low molecular weight oligomers, thermal degradation products) should be removed by hot ethyl alcohol (absolute) extraction rather than dissolution.

5. Finally, it would be very interesting to see to what extent the molecular weight and/or the crystallinity of the final polymer product could be further enhanced by solid-state post (additional) polymerisation and/or improved chain packing. This usually applies only to linear polyester condensates but it is possible that it could have some application to ring-opening polymers too.