POLYMERISATION OF CYCLIC DERIVATIVES OF α - HYDROXY ACIDS

by

Hussain Ali Al-Mesfer

A thesis submitted for the degree of

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of

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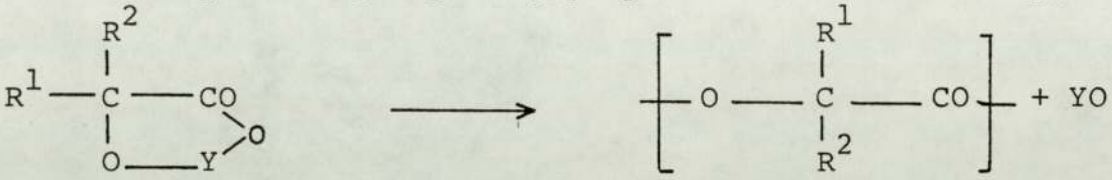
SUMMARY

This thesis is concerned with the improvement of the versatility of ring opening polymerisations of the type



(A)

Where Y is CO, SO or CS.

The aim of the work has been firstly to add to existing knowledge of, and information relating to, some initiation processes for these reactions and secondly, to increase the range of monomer structures and as a result polymers and co-polymers that may be formed. In particular it was hoped to obtain the necessary background information to enable copolymers containing functional groups at R^1/R^2 to be formed, since these are of potential biomedical interest.

The comonomers of particular use in this respect are those that can confer (a) strength and (b) biodegradability properties on the polymer. For this reason the dimethyl substituted anhydrocarboxylate (DMAC: A; $R^1=R^2 = CH_3$, Y = CO) and anhydrosulphite (HBAS; A; $R^1=R^2 = CH_3$, Y=SO) and the unsubstituted anhydrocarboxylate (GAAC; A, $R^1=R^2=H$, Y=CO) and anhydrosulphite (GAAS; A: $R^1=R^2=H$, Y=SO) derivatives of glycollic acid have been primarily employed together with the carboxyl containing monomers derived from tartronic acid (TAAS; A; $R^1=H$, $R^2=COOH$, Y=SO) and (TAAC; A; $R^1=H$, $R^2=COOH$, Y=CO).

The synthesis and purification of these monomers was accomplished together with a study of their polymerisation using aprotic base and alkoxide initiation. A number of polystyrene supported pyridines were also examined. The kinetics of these reactions have been examined using gas evolution techniques and their products examined by infrared absorption spectroscopy, x-ray analysis and G.P.C.

The synthesis of a series of cyclic monomers of the general form (A; Y=CS, ie 2-thioxo-1,3-dioxolan-4-ones) has been attempted by treating the corresponding ∝- hydroxy carboxylic acid or its metal salt with thiophosgene.

Although some success was achieved the products were difficult to obtain in a pure state.

KEY WORDS: ANHYDROCARBOXYLATE, ANHYDROSULPHITE, POLYMERISATION, SUPPORTED CATALYST, POLY - ∝ - ESTER

CONTENTS

LOCATION OF FIGURES

LOCATION OF TABLES

ACKNOWLEDGEMENTS

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This work was carried out between October 1977 and October 1980 in the Department of Chemistry of the University of Aston in Birmingham, under the supervision of Dr. B.J. Tighe. No part of this work has been submitted for any other award.

H. A. AL-MESFER

To my Mother and Father

I thank kindly my parents and my sister (HAIFFA) for their encouragement and support throughout this work.

CHAPTER 1

INTRODUCTION

This thesis is concerned with certain aspects of the polymerisation of cyclic esters, in particular those derived from α- hydroxy acids. Since ring - opening polymerisation is a large field, this introductory chapter is intended only to provide an outline of the overall scope of the subject with particular reference to the behaviour of cyclic esters. The particular aspect of the subject with which the work is associated is then dealt with in more detail (section 1.4).

1.1 Introduction

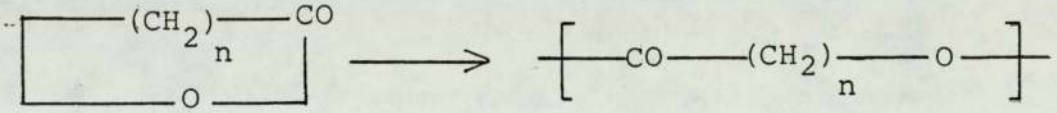
Ring - opening reactions as a route to the preparation of higher molecular weight compounds has been well known since the middle of the nineteenth century, when for example, the ring opening of ethylene oxide by Wurtz [1] and of glycollide (dimer of glycollic acid) by Bischoff and Walden [2] were described. The conversion of many cyclic compounds to polymers has been accomplished since that time by ring - opening reactions. In all of these reactions, the cyclic monomers contain at least one heteroatom or in a few cases unsaturation in which polymerisation occurs by a metathesis reaction.[3,4]

Ring - opening polymerisation is a mode of polymer formation which offers distinct advantages over conventional addition and condensation polymerisations. In many ways this polymerisation may be classed as a condensation reaction since the polymer formed has the structural features of a condensation polymer. By way of contrast the polymer in a number of cases has the same composition as the monomer and the polymerisation takes place by a chain growth mechanism. In addition

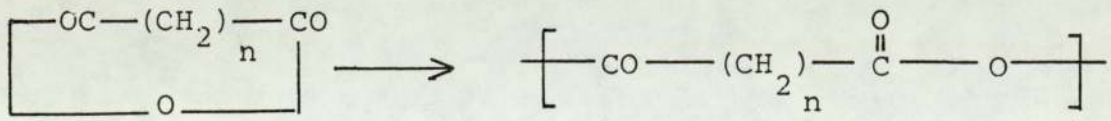
polymerisation, the monomer requires an active site and must be able to replicate the propagating species. Unfavourable equilibrium reactions between monomer, eliminated units and polymer are often encountered in condensation polymerisation whereas reversibility in ring - opening polymerisation is more akin to that in addition reactions. Thus ring - opening polymerisation may be considered as combining some of the advantages of an addition type mechanism in the formation of a heterochain polymer.

The polymerisation of a ring compound is usually induced catalytically (anionically or cationically) or by the presence of small amounts of end- group producing substances. Several reviews [5-8] on ring - opening polymerisation cover much information especially on the ring-opening polymerisation of lactones, lactams, epoxide and α- amino acid N - carboxy-anhydrides, but little on the aspects of the subject with which the work is concerned.

It is convenient to divide ring-opening polymerisation into two classes. In the <u>first type</u> no small molecule is split off in the reaction, as every element in the monomer is used to form part of a polymer chain, and the ring is in some sort of equilibrium with the chain eg:



Lactone



Cyclic Anhydride

Cyclic Ether

Dainton and Ivin[9] have studied the thermodynamics of this type of ring - chain equilibrium in terms of the equation :

$$T_c = \frac{\Delta H_p}{\Delta S_p^o + R \ln[M]}$$

Where :

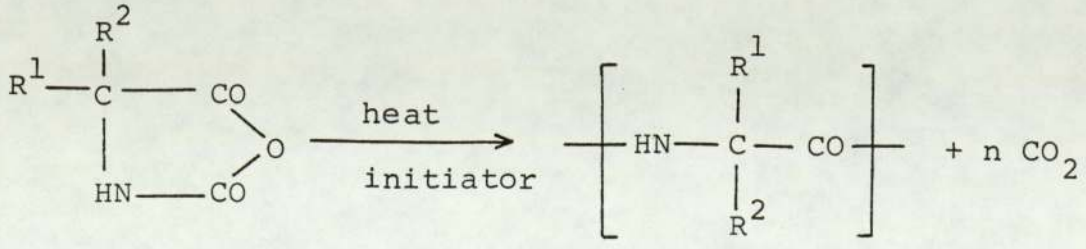
T_c = The ceiling temperature,

ΔH_p = The enthalpy change of polymerisation,

ΔS_p^o = The entropy change of polymerisation

For $[M]$ = 1 mole litre $^{-1}$.

The ceiling temperature may be defined as the temperature above which the formation of long chain polymers from monomer at concentration $[M]$ is impossible, or, in another way, it means the temperature at which the rates of polymerisation and depolymerisation are equal. Polymerisation by thermal methods alone are not often used, because the temperature required to achieve ring opening is often above the ceiling temperature. In the second type, a small molecule is eliminated during the polymerisation of the cyclic monomer, this type of reaction has been called an "extrusion polymerisation". [10] The ring - opening polymerisation of NCAs (I) is an example of this type of reaction, the small molecule is carbon dioxide which is evolved as gas and hence removed from the reaction medium.



(I)

N.C.A. .... (1.1)

In recent years "extrusion polymerisation" has received a considerable amount of attention. It has the advantage that there is no ring chain equilibrium between the polymer and the monomer, and consequently, there is no tendency towards the depolymerisation.

This contrasts with typical condensation polymerisation in which a small molecule is also eliminated but it is derived from both reactants, for example, the water is eliminated from dicarboxylic acid - diol polyester polymerisation.

1.2 General Principles

The polymerisation of cyclic monomers depends on the following factors :

(1) The nature and reactivity of functional groups or hetero-atom in the ring,

(2) ring size and the extent of a ring strain,

(3) the nature and number of ring substituents, and

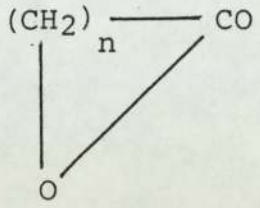
(4) the initiator and polymerisation conditions.

Ring strain is a thermodynamic property caused by either forcing the bonds between the ring atoms into an angular distortion (for three and four membered rings) or by steric interaction of neighbouring substituents on the ring (for monomers with more than five ring atoms) and it is dependent on the size and nature of hetero - atoms in the ring. The existence of ring strain in cyclic hydrocarbons is revealed by their heats of combustion.[11]

Comparable ring strains to those found in cyclic hydrocarbons occur in cyclic ethers, and, when strain exist, they constitute the principal driving force for the polymerisation[12] Replacement of a methylene group by an oxygen atom causes very little change in bond angle strain but reduces, somewhat,

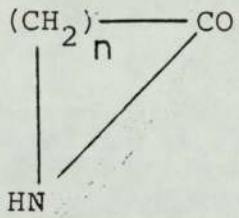
ring strain caused by steric interaction.

Hall and Schneider [13] have reported the polymerisabilities of cyclic compounds containing carbonyl groups, such as lactones (II). The five - membered ring will not



(II)

homopolymerise, whereas the six - membered ring polymerised quite readily. In contrast with lactams (III), the reverse

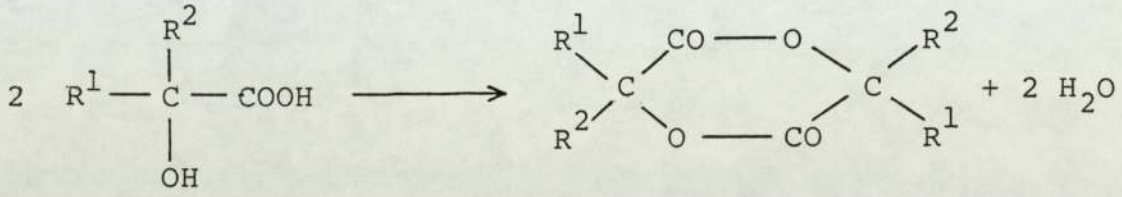


(III)

situation is observed. Small [14] has suggested that the change in free energy for the polymerisation of 5 - membered lactones is at a maximum for this class of monomer, whilst in the case of lactams, the maximum occurs with the six - membered ring.

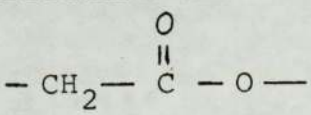
Carothers [15] has extensively studied the polymerisation of cyclic lactones (II) which are the most common class of cyclic esters. Cyclic lactones have been generated as intermediates by nucleophilic displacement [16], free-radical processes [17], thermal eliminations [18,19] and photochemical reactions [20]. Lactones (II) are usually formed by dehydration of hydroxy acids, by the action of acids or basis (e.g. H_2SO_4 or NaOH). The products of dehydration reactions are dependent on the number of carbon atoms between the hydroxyl and

carboxyl groups [21]. For example, ∝ - hydroxy acids (IV) dimerise when heated in the presence of a dehydrating agent to form the six - atom ring lactide structure (V) (or glycollide when $R^1 = R^2 = H$).

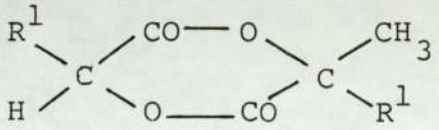


(IV) (V)

Lactide (V) is essentially symmetrical, as it has two identical R^1 groups and two identical R^2 groups on the six - membered ring. The compounds may be named by systematic nomenclature, for instance (V) when $R^1 = CH_3$, $R^2 = H$ is called 3, 6 - dimethyl - 1, 4 - dioxane, 2,5 - dione. When glycollide (V, $R^1 = R^2 = H$) is homopolymerised, the product is called homopolymeric poly (hydroxy acetic acid) or poly (glycollic acid) or poly glycollide. The individual units in the polymerisation are :-

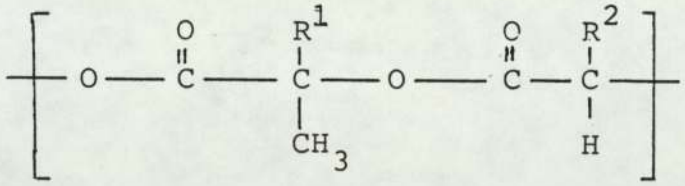


A recent patent [22] describes the preparation and polymerisation of an unsymmetrical lactide (VI).

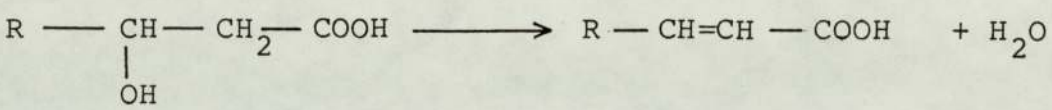


(VI)

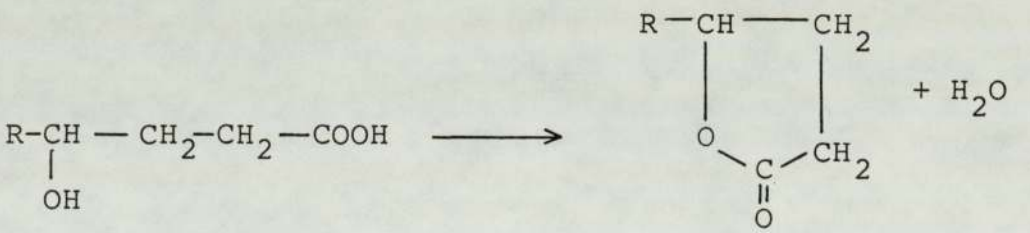
The polymers which are produced from (VI) contain the following recurring unit:



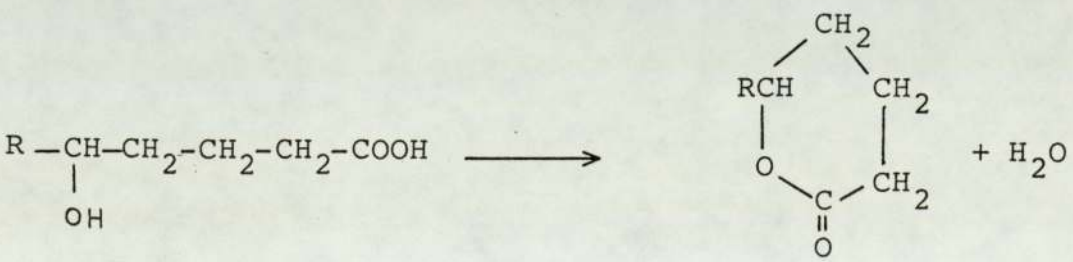
In contrast, the β - hydroxy acids (VI) yield, unsaturated acids on heating[23], not the lactone.



On the other hand, γ - hydroxy acids afford γ - lactone[24] (Equation 1.2) and δ - hydroxy acids afford unstable lactones (Equation 1.3) which are easily converted to linear polyesters[24,25].



.... (1.2)

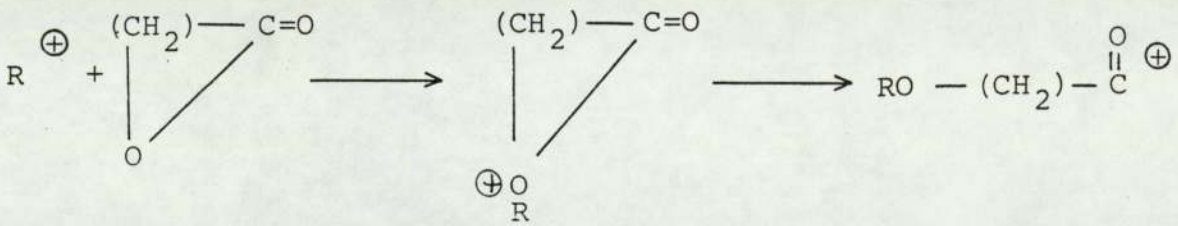


When the hydroxyl is more than six positions away from the carbonyl group only linear polyesters are obtained.[113]

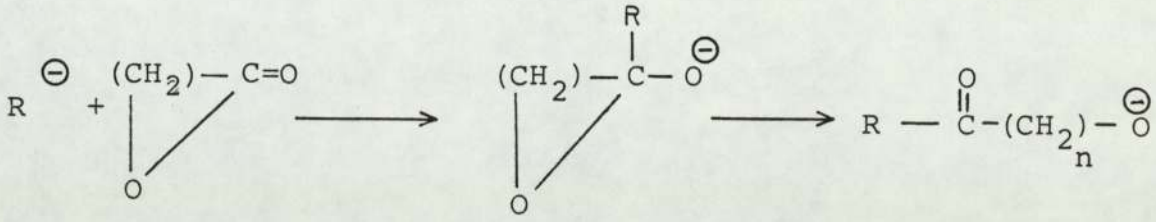
Some lactides (6 - membered rings) polymerise fairly readily by heat and zinc chloride [26 - 28] (e.g. glycollide; V: $R^1 = R^2 = H$). When $R^1 = H$ and $R^2 = CH_3$ however, polymerisation was more difficult, and with dimethyl substitution ($R^1 = R^2 = CH_3$), polymerisation did not occur [14]. However, Deibig [29] reported that 1, 1, 4, 4, tetramethyl glycollide, the dimer of α - hydroxy isobutyric acid (V: $R^1 = R^2 = CH_3$) could be polymerised at elevated temperature by using lithium tertiary butoxide as a catalyst to yield high molecular weight poly (isopropylidene carboxylate). There is considerable doubt as to the validity of this claim, however. In the polymerisation of lactones by alkoxides [30], there is an acyl oxygen cleavage in the ring, resulting from the attack of a nucleophile. However, these polymerisation are very slow at room temperature, and generally a temperature of at least $100^{\circ}C$ is required for a reasonable rate of reaction.

A great number of organometallic compounds, metals, Lewis acids, protonic acids and amines have been examined as catalysts for lactone polymerisation. There are two basic mechanisms for polymerisation of lactones : -

(1) Cationic polymerisation which involves the attack of the carbonium ion upon the lactone molecule with cleavage of the acyl - oxygen bond and generation of an acyl carbonium ion to continue the reaction and



(2) Anionic polymerisation which involves acyl - oxygen cleavage of the ring.

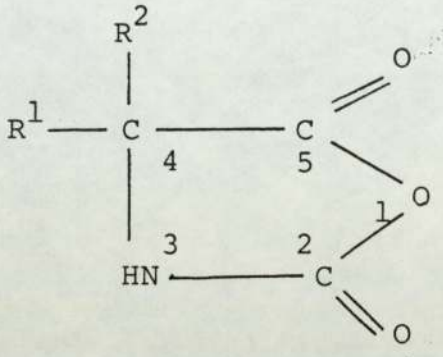


Lactonescan copolymerise with cyclic ethers such as epoxides and tetrahydrofuran. The copolymerisation with epoxides leads to the formation of copolymers containing ether and ester links in the chain.

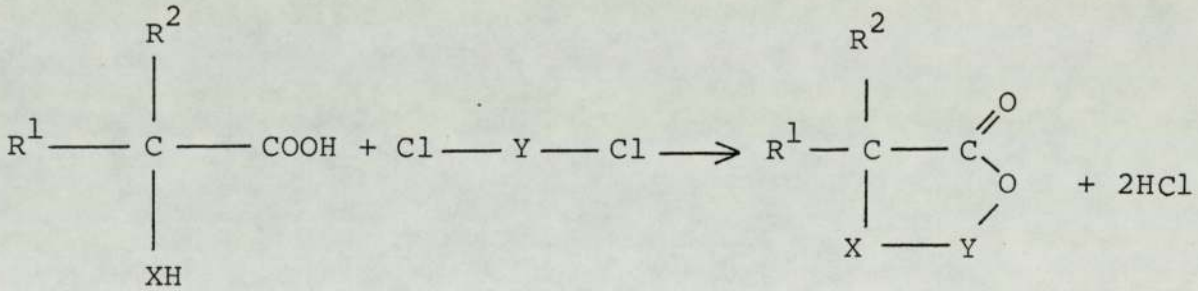
It can be seen therefore that lactone polymerisation presents a versatile route to homopolyesters and ester copolymers. There is however a major problem in the case of α - hydroxy acids since α - lactones are far too unstable to be formed directly and the preferred dimeric lactone (lactide) only undergoes polymerisation in the unsubstituted or monosubstituted cases. Because of this fact, it is relevant to consider monomers of type 2 (extrusion polymerisation) as possible routes to the polymers of α - hydroxy acids. The behaviour of monomers of this type is in many ways different from those of type (1) and will now be considered in some detail.

1.3 Cyclic Anhydrides of ∝- Functional Acids and Related Monomers

The earliest and best studied examples of monomers of type (2) were the cyclic anhydrides of ∝ - amino acids:



These compounds are however only one type of ring whose polymerisation takes place through the loss of some elements of the ring. A general scheme for the formation of these compounds is shown below



(VII)

Where:

X = CH_2, NH, O, S, Se, NR

Y = C = O, S =O, Se =O, C = S, C = Se

R^1, R^2 may be hydrogen, Alkyl, Aryl and their halogen substituted counterparts. The most important cyclic compounds of this type for ring - opening are shown in table (1.1).

Table 1.1

Some Examples of Cyclic Derivative of ∝ - Functional Carboxylic Acids

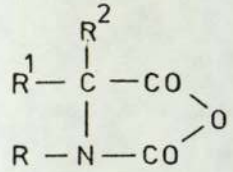
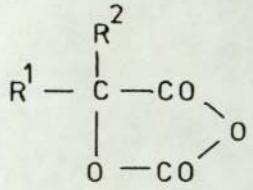
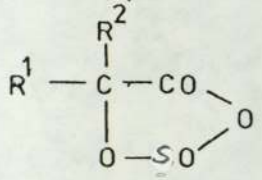
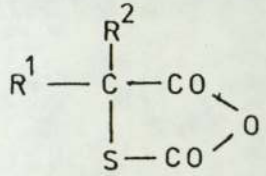
Ring Structure	General Name - common name - systematic name	Reactants	Expected Product
	∝ - amino acid anhydrocarboxylate 1,3 - oxazolidine - 2, 5 - dione	∝ - amino acid + Phosgene	Polypeptide
	(31.32) ∝ - hydroxy acid anhydrocarboxylate 1,3-dioxolan-2,4-dione	∝ - hydroxy acid + Phosgene	Poly - ∝ - ester
	∝ - hydroxy acid anhydrosulphite 1,3,2 - dioxathiolan-4-one-2-oxide	∝ - hydroxy acid + thionyl chloride	Poly - ∝ - ester
	∝ - thio acid anhydrocarboxylate 1,3 - oxathiolan - 2,5 dione	∝ - thio acid + Phosgene	Poly - thioester

Table (1.1) continued

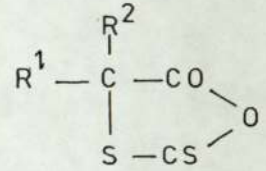
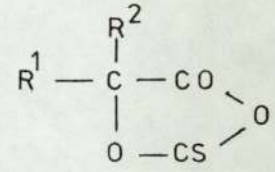
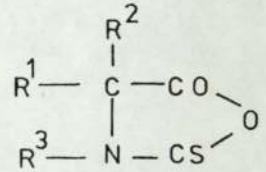
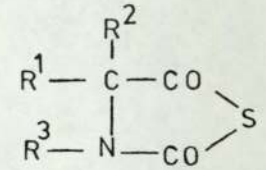
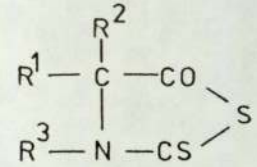
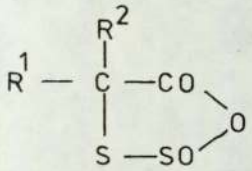
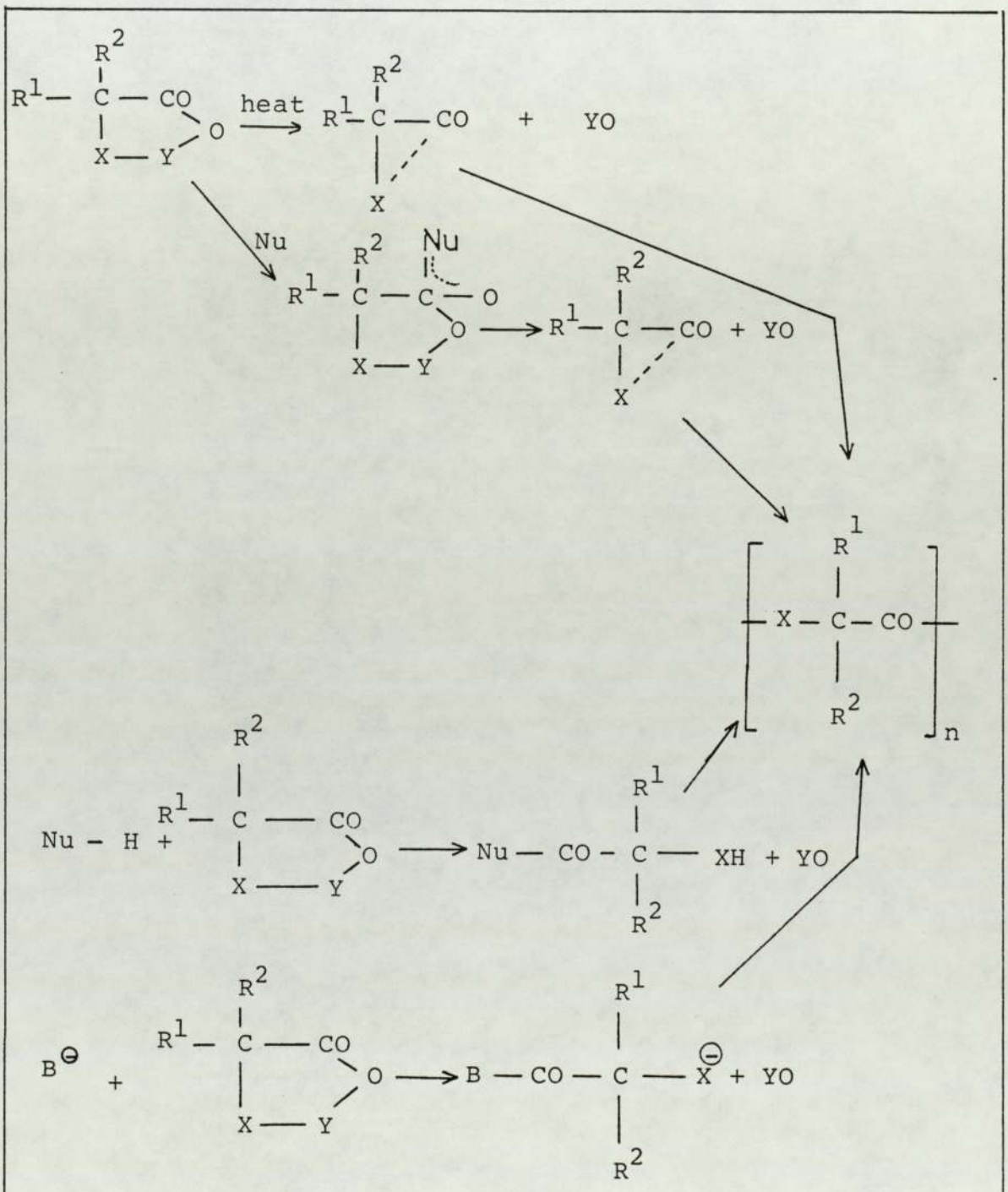
Ring Structure	General name	Reactants	Expected Product
	2 - thioxo - 1,3 - oxathiolan - 5 - one (33)	∝ - thio acid + thiophosgene	Poly - thioester
	2 - thioxo - 1,3 - dioxolan - 4 - one (34)	∝ - hydroxy acid + Thiophosgene	Poly - ∝ - ester
	2 - thioxo - 1,3 - oxazolidin - 5 - one	∝ - amino acid + Thiophosgene	Polypeptide
	2,5 - thiazolidin - 1,3 - dione (35,36)	∝ - amino thio acid + Phosgene	Polypeptide

Table 1.1 Continued

Ring Structure	General Name	Reactants	Expected Product
	2 - thioxo - 5 - thiozolidinone (37,40)	∝ - amino thio acid + Thiophosgene	Polypeptide
	∝ - thio acid anhydrosulphite (41) 1,2,3 - oxadithiolan -5-one-2-oxide	∝ - thio acid + Thionyl Chloride	Poly - thioester

Polymerisation of monomers of type (VII) to poly - ∝ - esters (where X would be - O -) can be achieved in principle by the routes shown in table (1.2).

Table (1.2)



The importance of the polymerisation of these compounds (i.e. related to VII) relies on the following points :

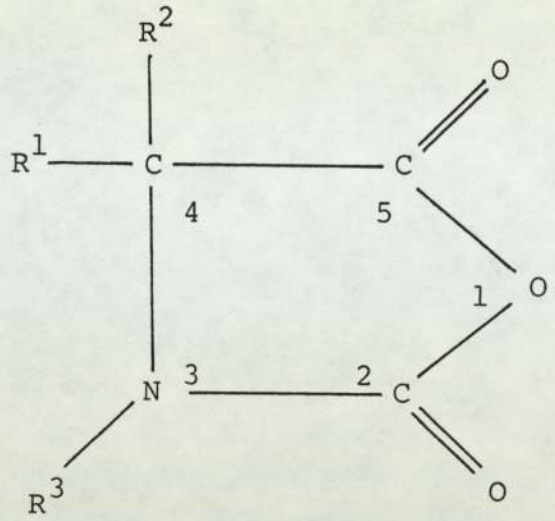
(1) Six member dimeric α- lactones (glycollides or lactides) polymerise with difficulty, and 1, 1, 4, 4 substituted six membered dimeric α - lactones do not polymerise. Therefore polymer products from these compounds can not be obtained. By using suitable R^1, R^2 groups in cyclic anhydride compounds, we can in principle obtain the corresponding polymers.

(2) Some of them form very good artificial silk fibres which are potentially reasonably cheap since the starting materials are cheap, eg. formation of NCAs from amino acid and phosgene.

(3) N.C.A.'s are very distinguished members of this category of monomers, since their polymerisation products, high molecular weight homo - and copolypeptide are useful models for studying the conformational properties of naturally occuring peptides and proteins.[42,43]

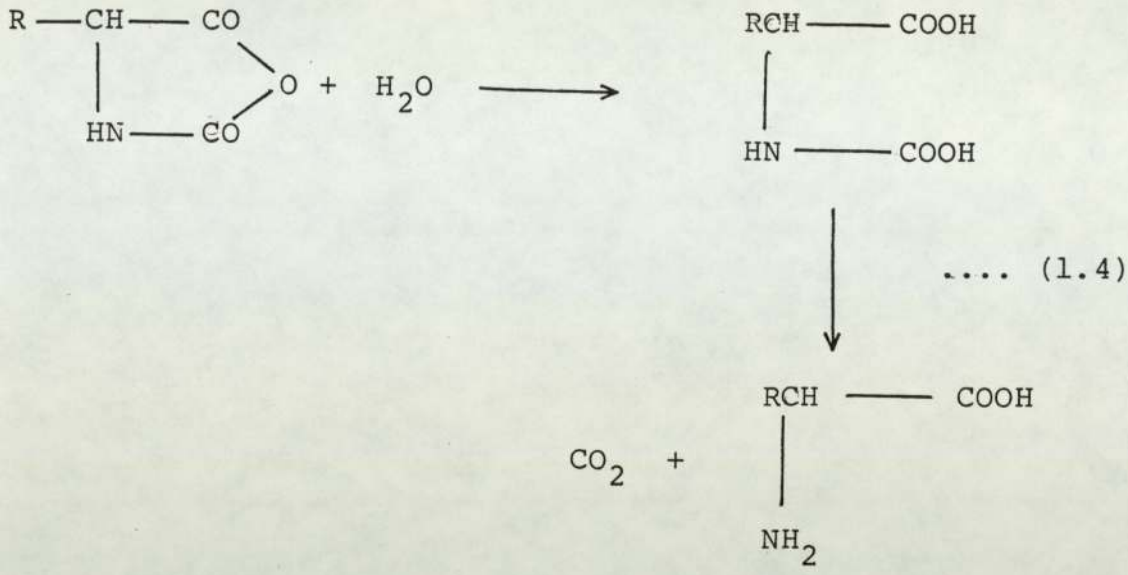
1.4 Previous Studies of NCA and Related Systems

Leuchs [44] in 1906 prepared the first α- amino acid carbohydrides (I) which were found to polymerise to poly - α - amino acids. The original name N - carboxy anhydrides (NCAs) is taken from ring system 1,3 - oxazolidine - 2,5 - dione[45] with the general formula shown over the page.



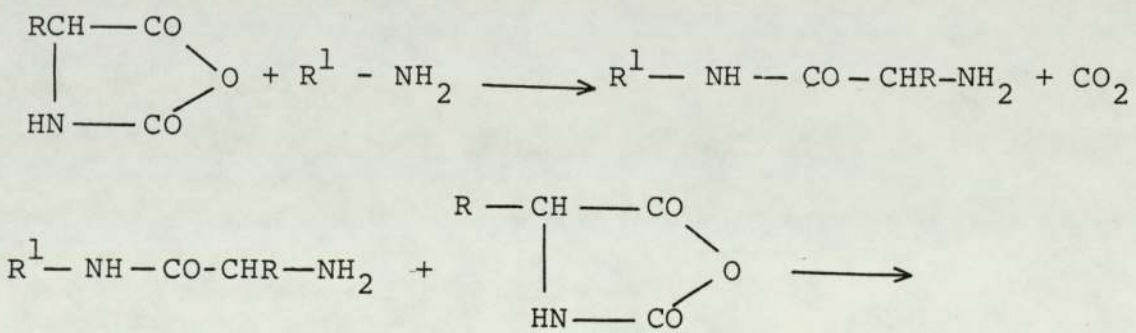
A large number of papers has been published on the polymerisation of ∝ - amino acid N - carboxy anhydride using various kinds of catalyst such as water [46], alcohols [47], amines [48] and alkali metal compounds [49–52]. In the case of alkoxide initiator, Idelson and Blout [51] have shown that the mechanism of decomposition proceeds by the action of the alkoxide on the C - 5 carbonyl of the NCA ring, followed by decarboxylation. It has been shown [53] that water catalysed the polymerisation of DL - phenyl alanine NCA in benzene at high temperatures. The reaction was first order only after a short induction period. The newly formed terminal group reacted with more monomer thus propagating the reaction.

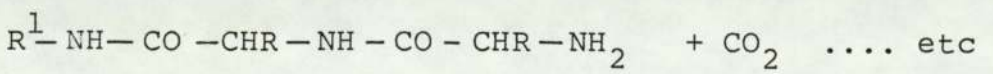
In the presence of primary amines, the polymerisation of N - carboxy anhydrides proceeds according to the so - called "normal" mechanism. The reaction is a multi - step nucleophilic attack by the terminal amino group on the 5 - carbonyl of the N - carboxyhydride, followed by ring opening and evolution of carbon dioxide. There is well - documented



.... (1.4)

evidence that in the "normal" primary amine - initiated polymerisation each amine initiated one polymer chain, so that the number - average degree of polymerisation is given by the molar ratio of monomer (or anhydride) to initiator. With the exception of a few cases reported in the literature (eg [54, 55]), the concentration of amino groups remain constant during the polymerisation, and is identical to the initial amine concentration.





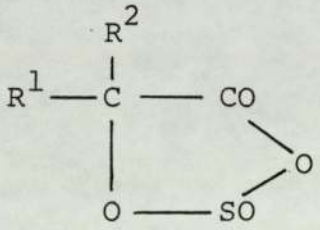
..... (1.5)

When the reactivity of the initiating amine is comparable to the reactivity of the terminal group of the growing chain, the polymerisation rate follows simple first - order kinetics :

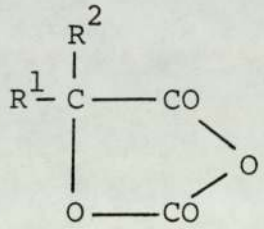
$$-\frac{d[M]}{dt} = k\,[M]\,[I]$$

in which the rate constants for the individual reaction steps are identical. Under these circumstances, both theoretical and experimental results indicate that a very narrow molecular weight distribution (poisson) is obtained. (56 - 58)

Other ring compounds, although structurally similar to NCA's, have received much less attention, for example anhydrosulphites of ∝ - hydroxy carboxylic acids (VIII) which are systematically named as 1, 3, 2 - dioxathiolan - 4 - one - - 2 - oxides, and anhydrocarboxylates of ∝ - hydroxy carboxylic acids (IX) known as 1, 3 - dioxolan - 2, 4 - diones.



(VIII)



(IX)

Anhydrosulphites (VIII) are synthesised by the action of thionyl chloride on an α- hydroxy acid. Blaise and Montague [22] first reported the synthesis of the anhydrosulphite of lactic acid (VIII; $R^1 = H$, $R^2 = CH_3$) and of α-hydroxy isobutyric acid (VIII; $R^1 = R^2 = CH_3$). Davies [59] first published work on the synthesis of anhydrocarboxylates of, α- hydroxy carboxylic acidsincluding (IX ; $R^1 = R^2 = H$; $R^1 = H$ $R^2 = CH_3$; $R^1 = H$ $R^2 = C_6H_5$) by direct reaction between parent acid and phosgene. These anhydrocarboxylates were purified by recrystallisation from anhydrous, low boiling solvents such as ether.

Tighe [60] attempted to synthesize anhydrocarboxylates of α - hydroxy carboxylic acids based on the work of Davies. Glycollic acid anhydrocarboxylate could not be obtained in pure state, but the author was successful in synthesizing lactic and mandelic acid anhydrocarboxylates although the methods for purification described by Davies such as crystallization were found unsatisfactory in the preparation of compounds of high purity. Modifications to the synthetic route and purification techniques were made which overcome these difficulties.

A series of papers has recently been published on the decomposition of both anhydrosulphites and anhydrocarboxylates with variations in R^1 and R^2 substituents as shown in Table 1.3.

TABLE 1.3

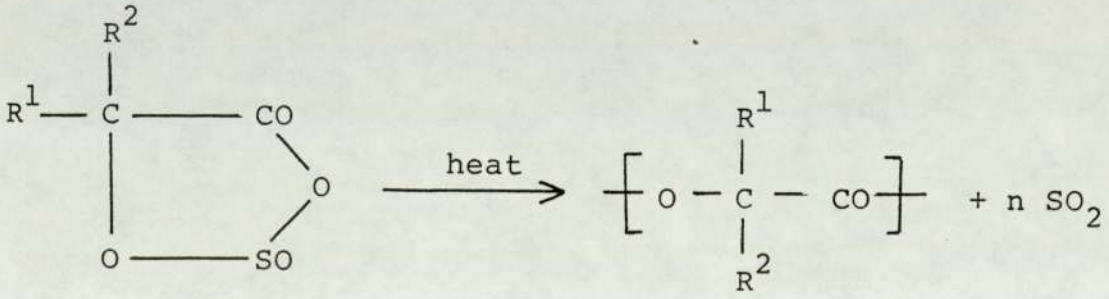
Substituents R^1, R^2	Reference
Hydrogen	61, 62
Simple alkyl	18, 19, 63 - 65
Cyclo alkyl	66 - 68
Aryl	69 - 71
Halo - alkyl	72, 73
Halo - aryl	74 - 76

1.5 Mechanisms of cylic anhydride ring opening

There have been three mechanisms postulated for the polymerisation of this class of cyclic compounds. These have been summarised in Table 1.2 .

1.5.1 Thermal Decomposition

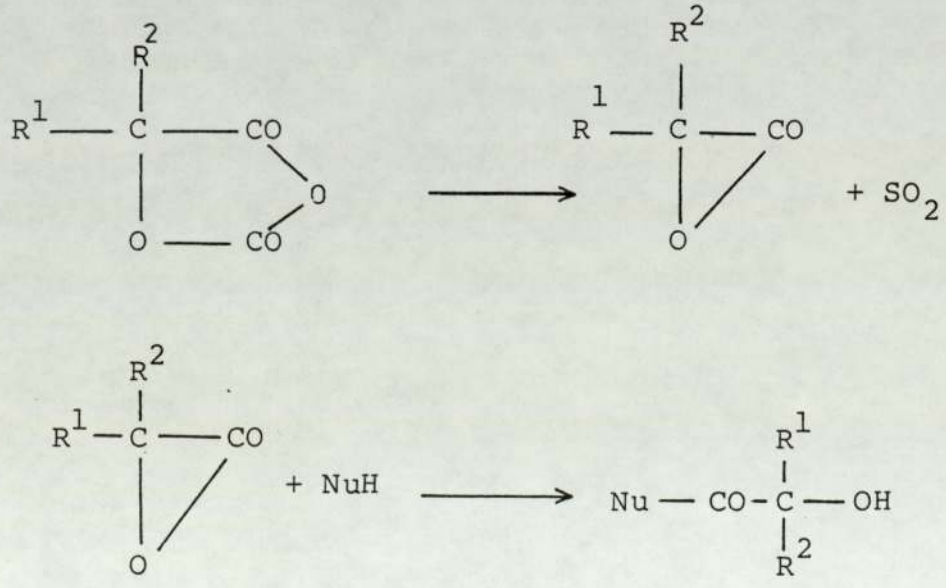
Anhydrosulphites of ∝- hydroxy carboxylic acid (VIII) have been known [61, 18, 77] to give poly - ∝ - esters of high molecular weight by thermal decomposition according to the following equation



.... (1.6)

Alderson [78] reported the polymerisation of ∝ -

hydroxyisobutyric acid anhydrosulphite (VIII :$R^1 = R^2 = CH_3$) in non - hydroxylic solvents (e.g. chlorobenzene , or benzene) and in the absence of initiators to give polymers with molecular weights in the region of 100,000. The temperature of the thermal decomposition of the anhydrosulphite to polymer was governed by the boiling point of the solvent. It was observed that the presence of moisture reduced the molecular weight of the polymers. The mechanism of polymerisation was subsequently studied by Ballard and Tighe [61]. This mechanism generally requires a thermally unstable molecule, and is typified by the thermal decomposition of the monomer to form a highly reactive α - lactone as an intermediate species, with a thermal elimination of sulphur dioxide from the ring. Polymerisation of the α - lactone, a species which has recently been isolated[79], is initiated by an adventitious trace of moisture or another nucleophile and is propagated by the hydroxyl group produced by the decomposition of the α - lactone.



..... (1.7)

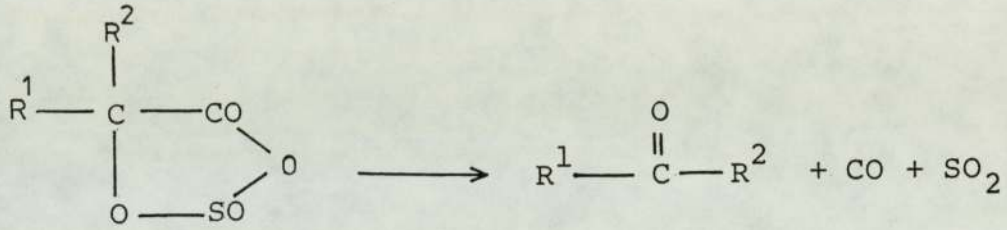
The rate of polymerisation is dependent upon the rate of primary ring scission, which involves concurrent expulsion of a gas molecule and the formation of a reactive α - lactone.

Of the various types of 5 - membered cyclic monomer, the anhydrosulphites (VIII)are more likely to polymerise thermally, because the extra ring strain imposed by the large sulphur atom in the ring, renders them more thermally unstable, and hence more likely to decompose to the α - lactone (in the case of α - hydroxy acid derivatives). The difference in stability of anhydrocarboxylates (IX) and anhydrosulphites (VIII) of α- hydroxy acids is due to the fact that the anhydrocarboxylate ring is planar, whereas the anhydrosulphite is puckered. This difference is well illustrated by considering the thermal decomposition of 5,5 - dimethyl - 1, 3, 2 - dioxathiolan - 4 - one - 2 - oxide (VIII: $R^1 = R^2 = CH_3$) [19] which has a half - life ($t_{\frac{1}{2}}$) of 3.5 hours at 90°c in nitrobenzene, and the 5,5 - dimethyl - substituted 1,3 - dioxolan - 2, 4 - diones (IX , $R^1 = R^2 = CH_3$) which is stable in these same conditions having a ($t_{\frac{1}{2}}$) of 1050 hours. Both anhydrocarboxylate and anhydrosulphite decomposition showed good first order behaviour with respect to residual monomer concentration.

The greater stability of anhydrocarboxylates is reflected in the mass spectra, where the anhydrocarboxylate rings all gave top mass peaks corresponding to the unfragmented ring. This was not observed with the corresponding anhydrosulphite [69].

However, both rings displayed a peak corresponding to the α - lactone.

The thermal decomposition of disubstituted anhydrosulphite increases as the size of substituents increases. With large substituents such as phenyl or strong electron withdrawing substituents a secondary fragmentation process occurs forming a ketone, carbon monoxide and sulphur dioxide.

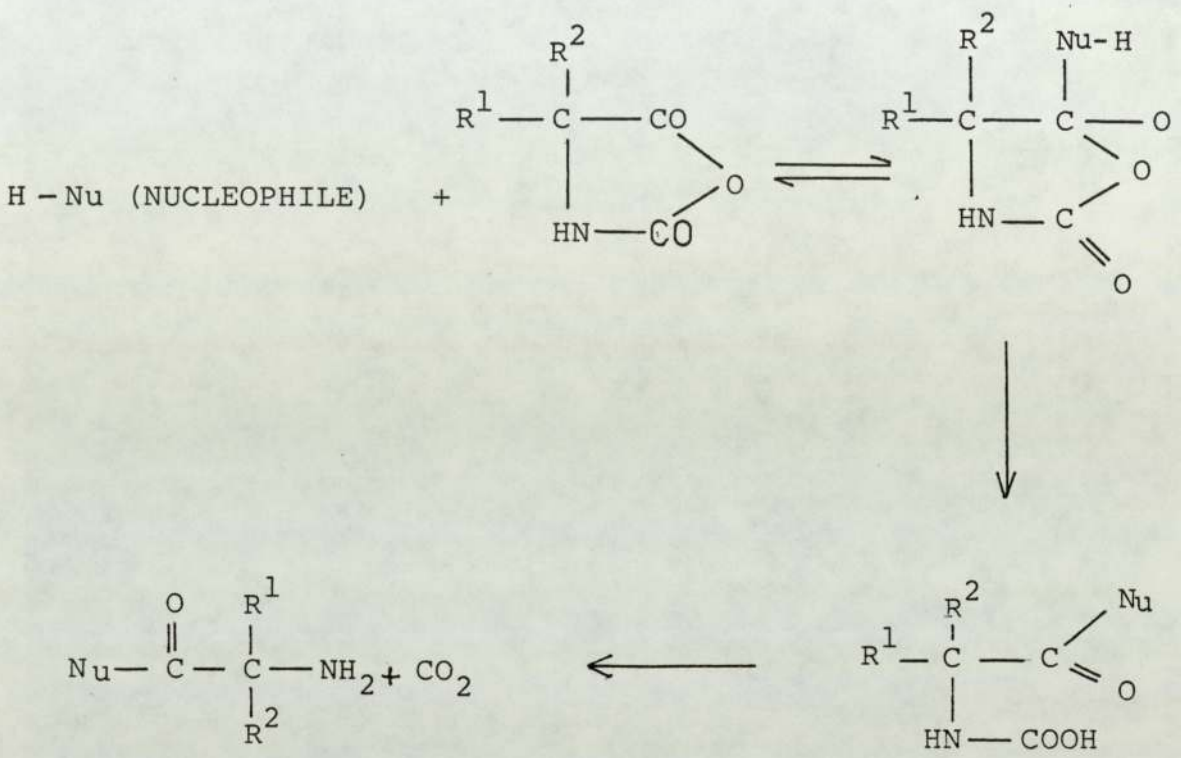


This competitive reaction is favoured at higher temperature for example during the thermal decomposition of bischloromethyl [73] and di n - butyl substituted anhydrosulphites [64]. This leads to difficulties in obtaining pure samples of monomer since the purification procedures tend to result in decomposition of these anhydrosulphites to non - polymeric products.

1.5.2 Protonic Nucleophilic Initiators

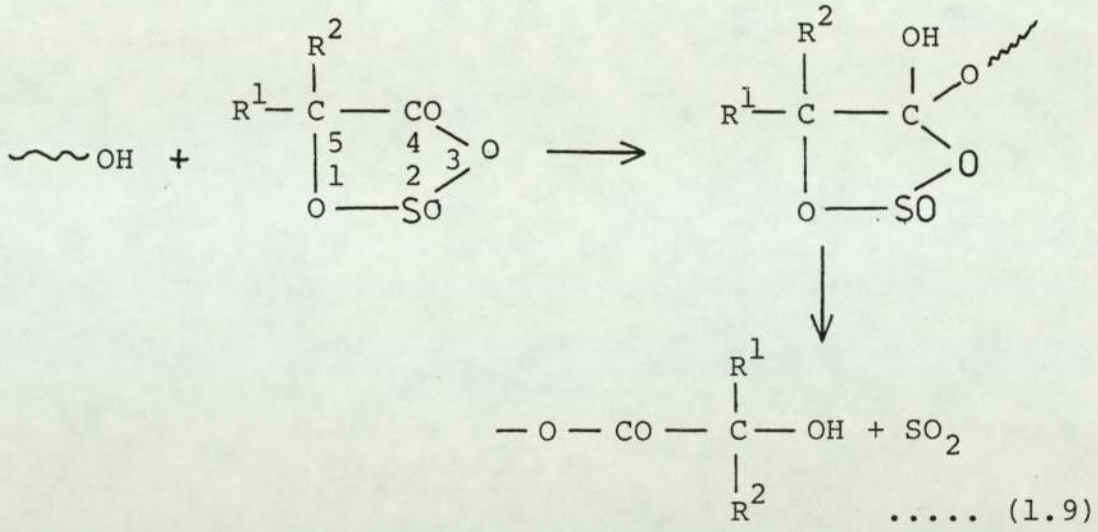
This mechanism is most frequently encountered in the amine initiated polymerisation of N - carboxy anhydrides. Anhydrosulphites (VIII and anhydrocarboxylates (IX) of α - hydroxy acids also undergo an analogous polymerisation mechanism, but this is limited by the reduced thermal stability of the ring, and the lower nucleophilicity of the

terminal hydroxyl group in the propagating species compared with amino group generated by NCAs (Equation 1.8)



..... (1.8)

In the case of anhydrosulphites in which at least one of the C - 5 substituents R^1 or R^2 is hydrogen, polymerisation can take place by a bimolecular hydroxyl - initiated propagation reaction [61, 62] analogous to the classic primary amine initiated polymerisation of N - carboxy - α - amino acid anhydrides [80].



..... (1.9)

In this reaction, the overall rate determining step is the direct attack of a terminal hydroxyl group on the C - 4 carbonyl group of the ring, (leading to polymer through the formation of a transition state). In anbydrosulphites with two alkyl substituents, steric hindrance inhibits this propagation reaction and polymerisation takes place via thermal decomposition.

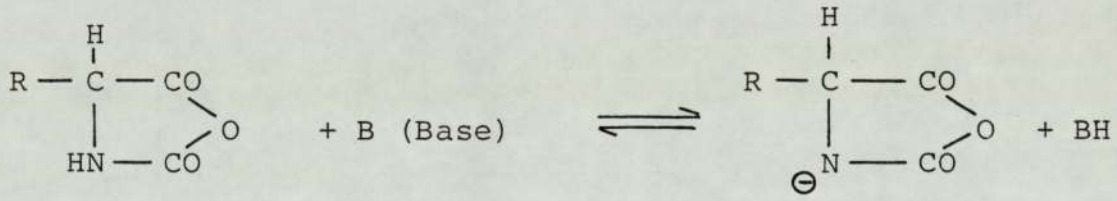
It is well known [72,75] in anhydrosulphite (VIII) and anhydrocarboxylate systems that the presence of bulky and of strongly electron - withdrawing substituents has a profound effect on the reactivity of the ring. Electron - withdrawing substituents have an activating effect on the C (4) carbonyl resulting in an increase in the susceptibility to nucleophilic attack. Primary and secondary amines are known to react with anhydrosulphite but amides, not polyesters are the products.

1.5.3 Aprotic Initiators

One of the most important methods developed for the preparation of high molecular weight polypeptides from N - carboxyanhydrides involves the use of strong base or

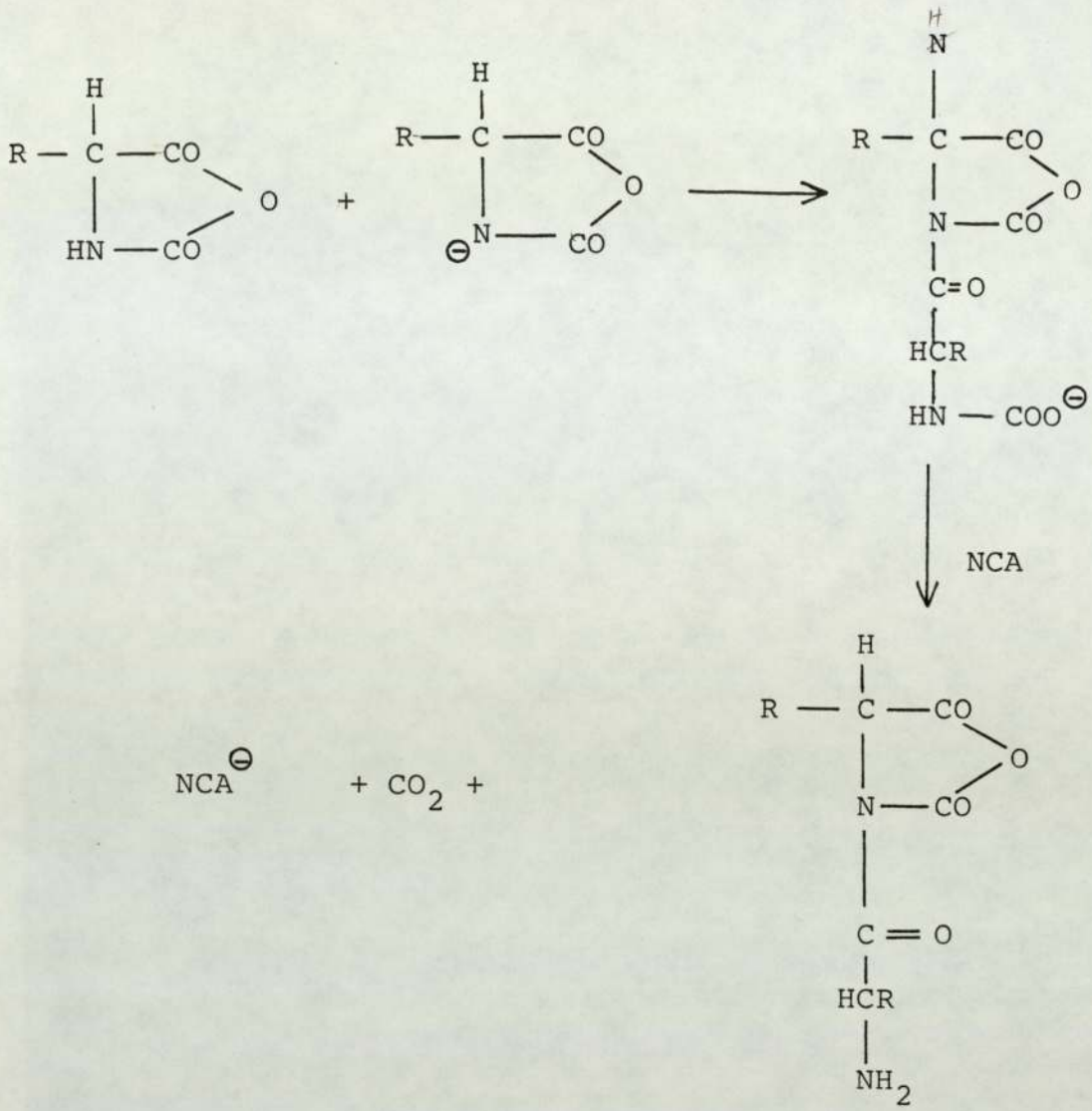
aprotic initiators. In the presence of initiators such as carbanions, alkoxides, alkaline hydroxides, and aprotic bases (such as tertiary amines), the polymerisation of N - carboxyanhydrides exhibits entirely different features from those observed for primary amine - initiated polymerisations. The reaction rate is much faster and the degree of polymerisation is much higher than the monomer - to - initiator molar ratio.

Bamford and Block[81] put forward a mechanism which was subsequently modified by Szwarc [82] and accepted in recent papers [83, 84]. According to this mechanism, the tertiary amine activates the NCA monomer by abstracting a proton from the ring nitrogen , rather than a nucleophile attacking the C (5) carbonyl.



.... (1.10)

The "active monomer", i.e. the N - carboxyanhydride anion, is responsible for very fast propagation according to the following series of reactions :



The chain grows by nucleophilic attack by "active monomer" of the cyclic end of the bifunctional intermediate to form a carbamate which abstracts from a proton from another N - carboxy anhydride molecule. This regenerates the "active monomer" which can then attack the cyclic end of the growing chain. The driving force for the polymerisation is the evolution of carbon dioxide. The polymerisation is anionic, with the negative charge not on the growing chain (as in vinyl anionic polymerisation) but on the "active monomer". This is completely analogous to the well - established "active monomer" mechansim for anionic polymerisation of cyclic lactams in the presence of strong base[85]. In this case, abstraction of the amide proton by the base yields lactamate anions, the active species responsible for the rapid chain growth.

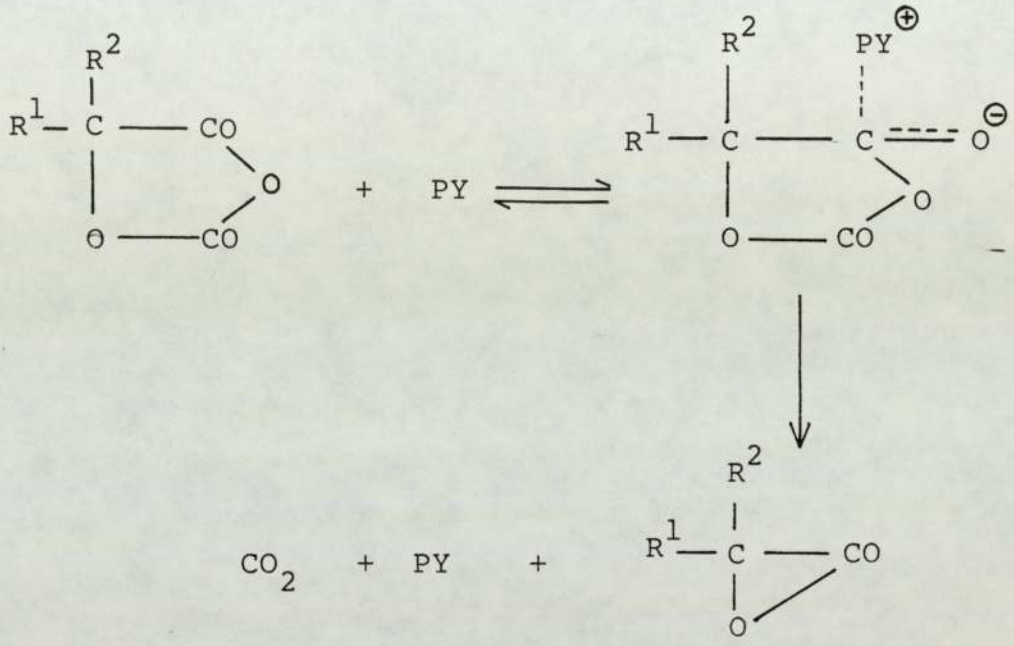
Bamford and Block[86] used a series of tertiary amines such as pyridine, ∝ - picoline and 2, 6 - lutidine for the initiation of the NCA polymerisation. The most effective of these is 2, 6-lutidine, the most basic amine in the series. This is a strong argument in favour of the initiation via proton abstraction (Equation 1.10) from the N - carboxy - anhydride rather than nucleophilic attack by the amine on the 5 - carbonyl monomer (Equation 1.8).

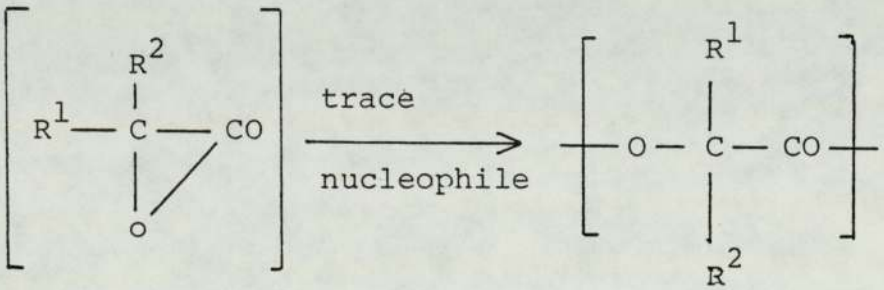
Initiated decomposition of anhydrosulphites has been reported [87] using such initiators as triethylamine, dimethyl-formamide(D.M.F.) , dimethyl sulfoxide (DMSO), and pyridine. Organo-metallic catalysts such as sodium methoxide, butyl lithium and zinc diethyl / water are also reported to polymerise anhydrosulphites. The polymerisation of methyl chloromethyl substituted anhydrosulphite with brucine is reported to give an optically active polyester[88].

Pyridine and various derivatives have been used as the catalyst in polymerisation of anhydrocarboxylatesof ∝ - hydroxy acid at different temperatures in nitrobenzene[89-91]. Tighe and Smith[92], have reported the use of tertiary organic bases such as pyridine in the polymerisation of 5 - phenyl - 1, 3 - dioxolan - 2,-4 dione(IX,R^1=H, R^2 = C_6 H_5).

A suggested mechanism for the decomposition of the anhydrocarboxylate with pyridine involves the attack of pyridine, acting as nucleophile, on the C -4 carbonyl of the ring producing a complex intermediate. Decomposition of this intermediate yields a polymerisable species, believed to be the highly reactive ∝ - lactone which takes part in a rapid chain propagation step with the terminal hydroxyl group of a polymer chain. Adventitious traces of

moisture regenerate a parent acid by hydrolysis of the ring, thereby providing initiation sites for this process. The reaction shows first order kinetics in both monomer



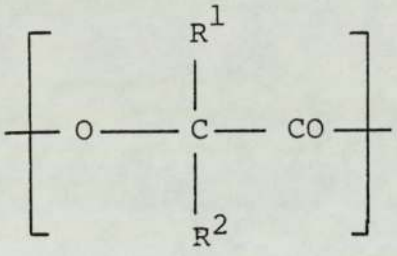


and base, and the fact that the molecular weight of the polymer is independent of the pyridine concentration.

Crowe[93] has reported that dialkyl substituted anhydrosulphites of ∝- hydroxy acids can be polymerised using an oganometallic catalyst system e.g. sodium methoxide and butyl lithium. The author studied the polymerisation of anhydrosulphite by lithium tertiary butoxide in decalin . The initial stages of the reaction were first order with respect to monomer and initiator concentration. The polymer produced from the polymerisation was found to have a lower molecular weight than that obtained by thermal decomposition methods.[94]

1.6 Nature of the Present Project

Poly-∝-esters (X) (which are generally defined as those polyesters in which only one main - chain carbon atom separates successive ester repeat units,i.e.



(X)

have until recently received comparatively little attention. One reason is the limited number of synthetic routes available. The most common synthesis is the direct self polyesterification of the appropriate ∝- hydroxy acid (or preferably ring opening of the relevant glycollide) in an inert solvent in the presence of an acid catalyst (e.g. orthophosphoric acid). This method, however, appears to be limited to glycollic and lactic acids since higher acids

produce unwanted by-products and polymers with only low molecular weights.

Poly ∝ - esters have been described as being potentially useful in many fields, including films, fibres, coatings and surgical inserts. In recent years poly (glycollic acid) and poly (lactic acid) (which are most readily synthesised poly - ∝ - esters) have received notable attention as biodegradable polymers for surgical sutures and other biomedical applications.

One of the aims of this project is to improve the versatility of ring opening polymeriastion and copolymerisation reactions in order to increase the range of poly - ∝ - esters availabilty, particularly for biomedical work.

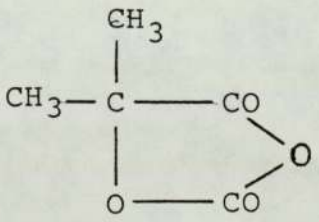
The aims of the work may be subdivided into two areas. Firstly, the study of methods of initiation in order to increase the scope of copolymerisation reactions. One reason for doing this is to find synthetic routes to copolymers of glycollic acid and substituted ∝- hydroxy acids other than lactic. Although glycollic - lactic copolymers can be synthesised from the respective glycollide mixture it is not possible to make for example glycollic - ∝ - hydroxy isobutyric acid copolymer in this way (as has previously been mentioned that 1, 1, 4, 4,-tetramethyl glycollide (V ; R^1 = R^2 = CH_3) will not polymerise). A similar problem exists with ∝ - hydroxy acid anhydrosulphites. The limited copolymer studies that have been carried out were based on thermal initiation. In this case it is the ∝ - hydroxy isobutyric acid that has by far the greatest reactivity ratio because of its relative thermal instability. The resultant polymers are substantially pure poly ∝ - hydroxy isobutyric acid.

It is hoped therefore that different methods of initiation will enable controlled copolymer synthesis to be obtained.

The second area is the synthesis of new cyclic monomers especially those containing functional groups since these will facilitate drug attachment to biodegradable poly - α - ester copolymers.

Turning again to the question of methods of initiation and polymerisation mechanism, the areas for study can be examined in more detail. Some are listed below.

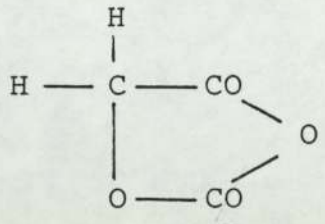
(1) An extension of studies of tertiary bases as initiators for α - hydroxy acid anhydrocarboxylates to the case where $R^1 = R^2 = CH_3$,



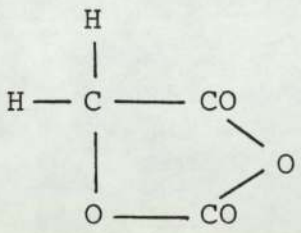
(XI)

to confirm that the mechanism holds in dialkyl substituted systems which have not been previously studied in this respect. In addition, to see if use of Taft equation enables the value of k to be predicted from polar and steric constant for CH_3 group. Tertiary bases are potentially useful for polymer formation particularly if they could be attached to a solid support, i.e. phase transfer catalyst.

(2) To investigate the use of alkoxide (and lithium tertiary butoxide in particular) in the cases of anhydrosulphites and anhydrocarboxylates of α - hydroxy acids (A, B and C) and compare with previous studies [93] of this initiator



A



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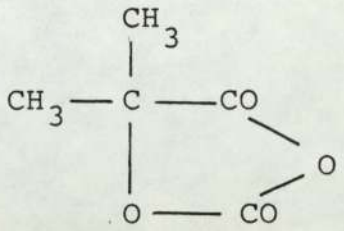

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with other anhydrosulphites. It is hoped that this will help to produce a more complete understanding of the way which alkoxide interacts with α - hydroxy acid derivatives and of the nature of the products.

(3) The thermal decomposition of anhydrosulphites has been the subject of a number of recent papers. The mechanism proposed by Ballard and Tighe [61] for the simple members of the series would appear to fulfil the general requirements for the thermal decomposition of this class of compounds.

This thesis investigates the effect of carboxyl groups attached to the anhydrosulphite ring on the polymerisability of the ring and hence evaluates the limits of this type of ring opening polymerisation as a route to carboxyl substituted poly - α - ester. The formation of polymers having specific arrangement of functional groups at the surface has potential value in the design of polymers for specific biomedical applications.

CHAPTER 2

EXPERIMENTAL METHODS

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2.1 Instrumental Techniques

Infrared Spectra - The Perkin - Elmer infrared grating spectrophotometers Models 237,297 were used. Samples were prepared as KBr discs in the case of solids and as thin films between NaCl discs in the case of liquids or solutions using air as a reference.

Mass Spectrometry - An AEI MS9 instrument was used for recording mass spectra.

Nuclear Magnetic Resonance Spectra - Proton spectra in the majority of cases were recorded using a Perkin - Elmer R 12 B spectrometer operating at 100 MHZ and of ambient temperature 33.4° C. Tetramethylsilane was used as internal reference for recording proton resonance spectra. Details of solvents and concentrations are given with specific examples in the text.

Temperature Controlled Water Baths - The Townsend and Mercer E 270 Bridge - Controlled Thermostat bath, with relay - heater systems within an accurate temperature of ± 0.5°C was sued for the kinetic experiments. Risella oil was used for temperatures up to 80° C.

Carbon / Hydrogen Analysis - The instrument used was a Perkin - Elmer 240 B carbon, Hydrogen, Nitrogen Analyser. The operating furnace was 1100° C.

Gas Liquid Chromatography - A Pye Gas Chromatograph series 104 together with katharometer detector was used. An E30 column consisting of silicone gum on firebrick was used and the carrier gas was helium..

X - Ray Photographic Analysis - X-ray powder photographs were taken using a Philips 11.46 cm diameter powder camera. The samples were mounted in lithium beryllium borate tubes and the X - rays generated from copper target at 40 KV.

Thermogravimetric Analysis (T.G.A.) - The instrument used was a Stanton Automatic Thermo - Recording Balance.

Dry Box Manipulations - Because of the sensitivity of the monomers and some intiators towards atmospheric moisture it was often necessary to carry out manipulations in a dry atmosphere. A glove box manufactured by SLEE (South London Electrical Equipment) Figure (2.1) was used for this purpose. Atmospheric moisture was initially removed by replacement of the air with dry nitrogen, followed by circulation of the atmosphere in the dry box through four glass coils immersed in a solid carbon dioxide /acetone mixture at-78^{o}C. The pumping rates of 6 l. min.$^{-1}$ through the main chamber and 4 l. min.$^{-1}$ through the access chamber were found to be suitable. In addition, regular replacement of drying agents such as molecular sieve type 5A (BDH Ltd.) and phosphorus pentoxide were used to maintain the dry atmosphere when the pumps were not in use. The atmosphere was regularly checked by a Shaw

Figure 2.1 Dry Box

Hygrometer connected to a Red Spot (sensitive) Type Element which was fitted to the main chamber of the glove box. This element was effective over the range 1-500 ppm(V/V) water.

Gel Permeation Chromatography (G.P.C.)

Molecular weight determinations of all polymers or decomposition products were carried out by the Gel Permeation Chromatography service run by the polymer supply and characterisation centre [95] of R.A.P.R.A., Shawbury, Shrewsbury. Molecular weight data as supplied were based on the assumption that the polymer (poly - α - ester) "behaves" as polystyrene in solution. In order that a reasonably accurate assessment of the molecular weight of poly - α - ester samples could be made "Q factors" were calculated for each poly - α - ester.

Where 'Q factor' = weight per A° length of the polymer assuming planar zig-zag configuration.

Q factor for polystyrene = 41.4

Q factor for poly DMAC = 21

Hence, m.w. of poly DMAC = m.w. of polystyrene $\times \frac{21}{41.4}$.

The principal of G.P.C . is based on the separation of polymer samples into fractions by using chromatographic column filled with rigid porous 'gel', highly crosslinked porous polystyrene particles. As the dissolved polymer molecules flow past the column they can diffuse into the internal pore structure of the gel to an extent depending on their size and the pore-size distribution of the gel. Larger molecules dissolved in the solvent carrier, cannot diffuse into the pores, and are rapidly eluted, while the smaller ones penetrate a large fraction of the interior of the gel. Thus the large

molecules leave the column first and the small ones last. The different molecular species are eluted from the column in order of their molecular weight.

Determination of Chlorine Containing Impurity

The concentration of ionisable chlorine in the sample of anhydrocarboxylate and anhydrosulphite was determined by potentiometric titration using a method modified from that due to Ingram.[96].

Approximately 0.1g of material was weighed accurately and 40 ml of 3:1 (V/V) mixture of distilled water and acetone plus a few drops of dilute nitric acid were added. The mixture was heated to 60°C for three minutes and then allowed to cool to room temperature. The solution was titrated potentiometrically with 0.01 N silver nitrate solution using a silver/silver, silver nitrate electrode / system in conjunction with an E.I.L. Model 23A pH meter. Calibration was first carried out using standard sodium chloride solutions. The end point being determined by graphical method. Hence the method effectively determines the predominant impurity which has been shown to be an α- chloro acid chloride.

2.2 Practical Techniques

Vacuum Sublimation

The apparatus used is shown in Figure(2.2). It was baked in an oven at 120°C for several hours before use and then transferred into the dry box and allowed to cool. The crude anhydrocarboxylate was placed in position A, then cold

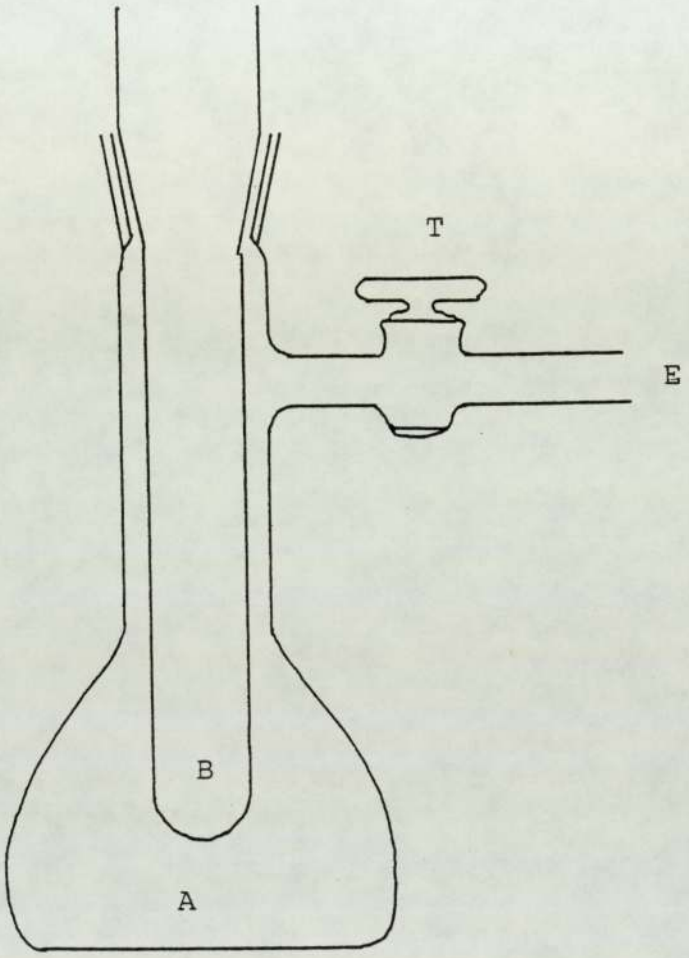


Figure 2.2 Vacuum Sublimation Apparatus

finger B was replaced and tap T closed. The apparatus was then removed from the dry box and evacuated via vacuum line E. The lower part of the chamber A was immersed in a water bath at a temperature $3^{o}C$ below the melting point of the anhydrocarboxylate. After the apparatus had been evacuated by opening of the tap T, a crushed solid carbon dioxide mixture was placed in a cold finger B at the bottom of which pure sublimed anhydrocarboxylates collected.

When the sublimation has been completed, tap T was closed and the apparatus allowed to stand to attain room temperature. The outside of the apparatus was then dried by a hot-air blower before it was placed in a dry box when the purified anhydrocarboxylate was removed and collected.

Polymerisation Techniques

(a) Techniques of Kinetic Measurement

Decomposition of anhydrocarboxylates and anhydrosulphites are accompanied by the evolution of the gases carbon dioxide and sulphur dioxide respectively. The rate of decomposition can, therefore , be followed by monitoring the increase in pressure of evolved gas with time at constant volume and temperature. The apparatus shown in Figure (2.3) was used for low temperature polymerisation. It was baked in an oven at $120^{o}C$ for three hours before use and then allowed to cool. Mercury was added via outlet A and made to fill reservoir C up to about half-full. Then opening A was closed by a suba-seal and tap D opened (having being previously connected to a vacuum line) so that the apparatus could be evacuated. During the evacuation the apparatus was

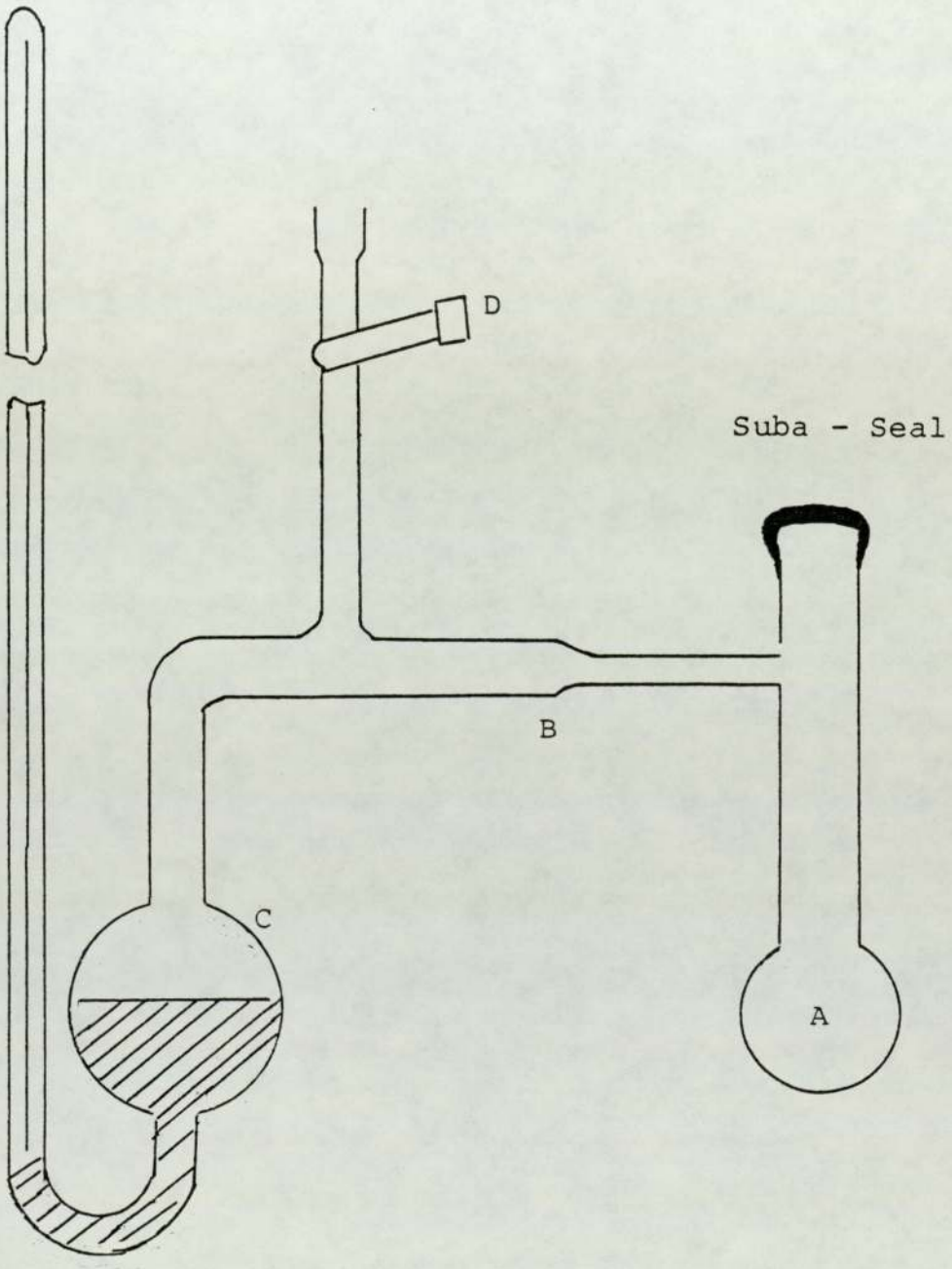


Figure 2.3 Low Temperature Kinetic Apparatus

flamed out to eliminate any moisture present. After cooling, the required amount of monomer solution, measured by syringe, was introduced into the reaction chamber. The apparatus was clamped in position in the water bath and the initiator was introduced as quickly as possible by injection through the suba-seal. The level of mercury in the manometer was followed by means of a cathetometer. Before each reading the apparatus was agitated with a 'Pifco' vibrator to equilibrate the concentration of evolved gas in the solution and in the gas phase. The reaction was allowed to proceed until no further increase in the height of the mercury column was observed. The reaction mixture was removed by syringe so that an infra-red spectral analysis could be made of the products.

For high temperature polymerisation kinetic work the apparatus shown in Figure (2.4), designed by Tighe[60] was used. It consists of a Chamber A where the polymerisation takes place, a mercury reservoir B and capillary C. This type of apparatus was found to be very useful, especially with regard to minimum number of joints, thus avoiding any leakage. Evacuation was effected by connecting the side arm (D) to a vacuum line and the apparatus isolated by sealing the capillary tube with an oxygen / gas torch.

The monomer solution was introduced into the apparatus by means of a hypodermic syringe. The mercury level in manometer Section C was followed by means of a cathetometer in which before

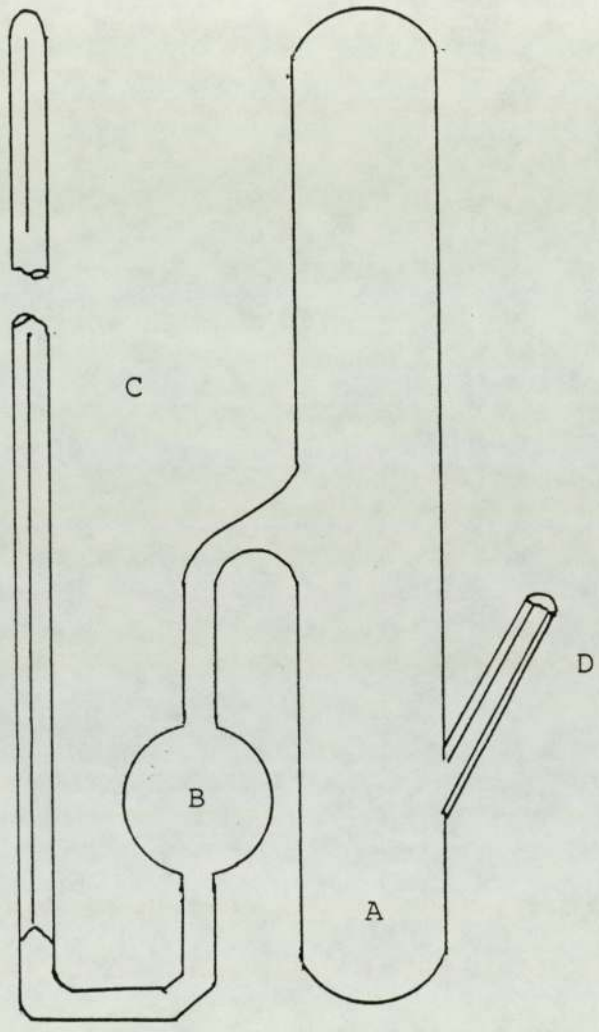


Figure 2.4 High Temperature Kinetic Apparatus

each reading the gas was allowed to equilibrate in the liquid and gas phases by use of a Pifco vibrator.

A simple relationship can be derived between the gas evolved and the concentration of monomer at any time during the decomposition.

If $[M]_o$ is the initial monomer concentration.

$[M]$ is the monomer concentration at any time

$[G]$ is the concentration of evolved gas at any time.

Then if one mole of monomer decomposes to give one mole of evolved gas:-

$$[M]_o = [M] + [G] \qquad \ldots\ldots\ldots (2.1)$$

on completion of reaction the equation simplifies to :-

$$[M]_o = [G]_\infty \qquad \ldots\ldots\ldots (2.2)$$

For an ideal gas in a system at constant volume and temperature the pressure P of the gas is directly proportional to the number of moles of gas evolved, that is,

$$P \propto [G] \qquad \ldots\ldots\ldots (2.3)$$

Hence $$P_\infty \propto [G]_\infty \qquad \ldots\ldots\ldots (2.4)$$

Therefore $$\pi P_\infty = [G]_\infty = [M]_0 \qquad \ldots\ldots\ldots (2.5)$$

Where π is a constant of proportionality.

If P is the pressure of gas at any instant, equation (2-5) may be written as:

$$\pi P = [G] = [M]_0 - [M] \qquad \ldots\ldots\ldots (2.6)$$

Combination of equations (2 - 5) and (2 - 6) then gives an expression for the fraction of monomer remaining : -

$$\frac{[M]}{[M]_o} = \frac{P_\infty - P}{P_\infty} \qquad \ldots\ldots\ldots\ldots (2.7)$$

or for the fraction of monomer reacted : -

$$\frac{[M]_o - [M]}{[M]_o} = \frac{P}{P_\infty} \qquad \ldots\ldots\ldots\ldots (2.8)$$

There are three requirements for these equations to function properly. First the temperature of the bath must be maintained at constant temperature throughout the reaction. Secondly, the volume of the reaction vessel should not change and finally the evolved gas must be near to ideal.

Equations 2.7 and 2.8 are used to calculate rate data and kinetic parameters as follows: From the first order kinetic rate equation (Wilhelmey equation) :

$$[M] = [M]_o e^{-kt} \qquad \ldots\ldots\ldots (2.9)$$

Where k is the rate constant

and since :

$$\log \frac{[M]}{[M]_o} = - kt \qquad \ldots\ldots\ldots (2.10)$$

A semi - logarithmic plot of $\log \frac{P_\infty - P}{P_\infty}$ against time should yield a straight line. First order rate constant k_1 can be

obtained by using half - life method when $(P_\infty - P)/P_\infty = 0.5$

and k_1 is calculated from

$$k_1 = \frac{0.693}{t_{\frac{1}{2}}} \qquad \ldots\ldots\ldots (2.11)$$

Where $t_{\frac{1}{2}}$ is the half - life in seconds. For a reaction which is first order in both monomer and initiator the rate of reaction is proportional to both the monomer and initiator concentrations.

$$-\frac{d[M]}{dt} = k_2 [M][I] \qquad \ldots\ldots\ldots (2.12)$$

For different initiator concentration, a first order rate constant k_1 is used from the expression : -

$$k_1 = k_2 [I]$$

and equation (2.12) becomes : -

$$-\frac{d[M]}{dt} = k_1 [M] \qquad \ldots\ldots\ldots (2.13)$$

Knowing k values at different temperatures, E_a (activation energy), A (frequency factor) and $\Delta \overset{\ddagger}{S}{}^*$ (entropy of activation) can be obtained from the relationship:

$$k' = A\, e^{-\frac{Ea}{RT}} \qquad \ldots\ldots\ldots (2.14)$$

Ea can be calculated, by plotting log k' against 1/T, and $\Delta S^{\ddagger}$ (entropy of activation) can then be calculated from the expression:-

$$A = \frac{KT}{h} e^{\frac{\Delta S^{\ddagger}}{R}} \quad \ldots\ldots (2.15)$$

Where K is Boltzman's constant (1.38×10^{-23} $J.K.^{-1}$)

h is Plank's constant (6.626×10^{-34} Js)

R is Gas constant (1.98 cal. deg^{-1}. mol^{-1}.)

(8.31 J. K^{-1} mol^{-1})

b) Polymerisation under reduced pressure

The type of carius tube in which the polymerisation under reduced pressure was carried out is shown in Figure (2.5). Each tubes was equipped with a B14 "quickfit" neck and had a fairly well drawn-out narrow stem in order to facilitate sealing off under vacuum. The tubes were heated in an oven for a few hours before use and then placed in a dry box. Polymer samples prepared by the thermal and catalysed decomposition of anhydrosulphites and anhydrocarboxylates was introduced into carius tube under anhydrous conditions using a dry box. The tube was then transferred to a vacuum line and evacuated to 0.5 - 1.0 mm Hg via B14 neck. It was then sealed using an oxygen / gas coal torch. Where a volatile solvent was to be used, the solution was frozen in liquid nitrogen before evacuation and sealing . After evacuation the tube was then placed in a constant temperature bath at the required temperature to complete the polymerisation.

(C) Polymerisation at atmospheric pressure

The apparatus shown in Fgiure (2.6) was used for this purpose. It was fitted with an inlet tube for dry nitrogen gas and a condenser with a drying tube packed with calcium chloride and cotton wool (loose) in order to prevent access of moisture. The monomer solution was introduced into the three neck round flask under a dry condition by using a dry box. The flask was then placed in a constant temperature bath and the initiator injected through the suba - seal by means of syringe. Nitrogen gas was slowly and continuously passed through the apparatus via the inlet A and the outlet C. Polymerisation samples at various reaction times, were removed by means of a syringe through a suba - seal.

2.3 Purification of Solvents and Reagents

The most important requirement for the purification of solvents and reagents used in the preparation and reaction of cyclic monomers was the complete removal of trace amounts of water. The techniques are described in practical organic chemistry textbooks[97,98]. Where distillation was to be carried out at atmospheric pressure or under reduced pressure a dry nitrogen atmosphere was used, vented to air through calcium chloride tubes to prevent entering of moisture.

Diethyl Ether - Diethyl ether anhydrous A.R. grade supplied by Fison Scientific Apparatus Limited (water content 0.02%) was used and stored over sodium wire.

Nitrobenzene - The A.R. grade of nitrobenzene supplied by Fison Scientific apparatus limited was allowed to stand over

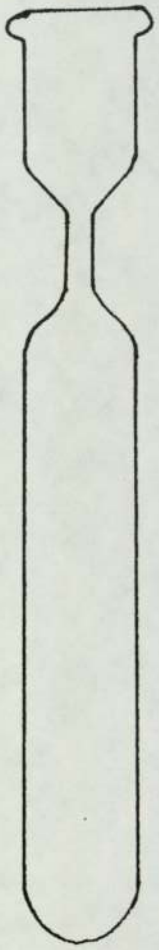


Figure 2.5 Carius Tube

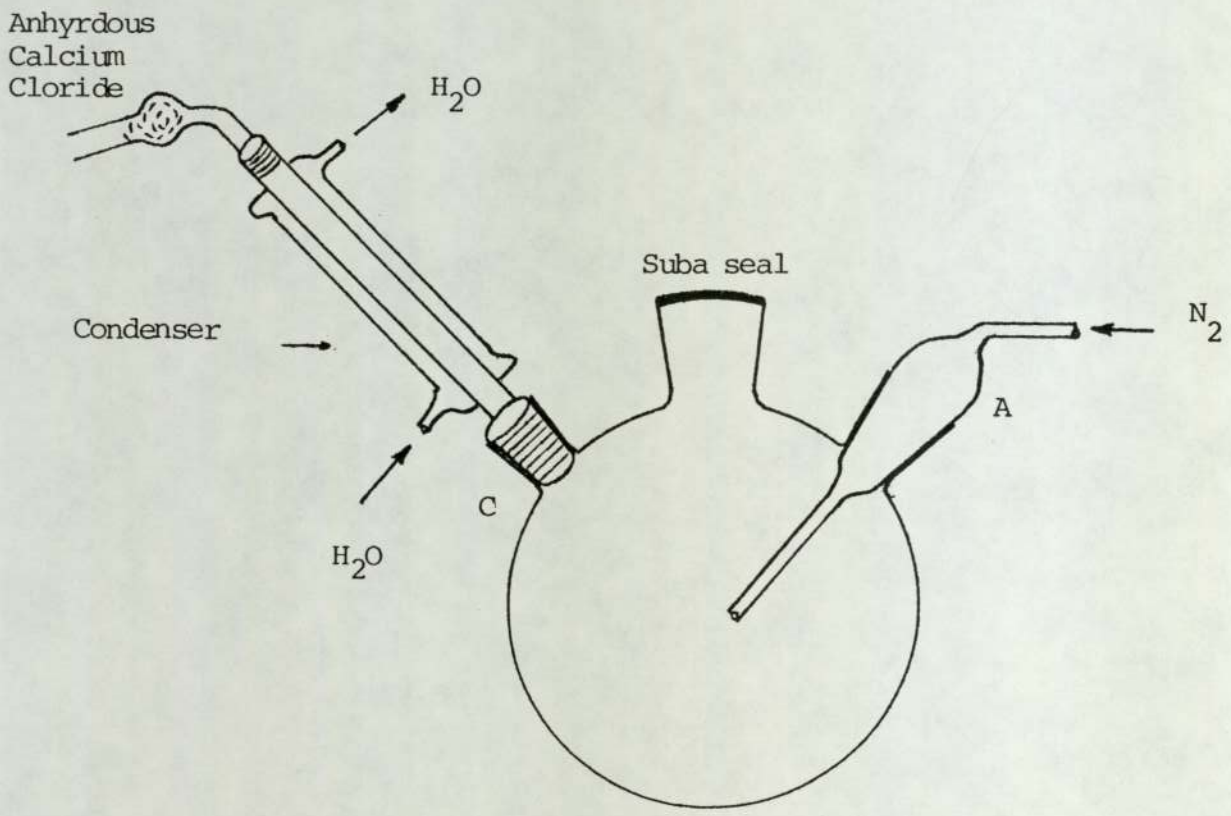


Figure 2.6

phosphorus pentoxide and then refluxed for twenty four hours. It was then distilled under reduced pressure using a dry nitrogen bleed system. The middle fraction was collected over anhydrous barium oxide. The solvent was kept in a dry box and distilled under reduced pressure prior to use. The middle fraction, boiling at 70°C / 0.5 mm Hg was collected.

Lithium Tertiary Butoxide - The reagent supplied by EGA-CHEMIE was stored in a dry box and used without further purification.

Toluene - The solvent was distilled at atmospheric pressure with precautions for exclusion of moisture. The distilled toluene was then refluxed over sodium wire for twenty four hours, followed by distillation. The distillate was stored over sodium wire. The solvent was re-distilled before use.

Pyridine - The anhydrous grade of pyridine supplied by B.D.H. Limited, with a maximum water content of 0.02%, was refluxed with analytical grade potassium hydroxide for twenty four hours with precautions for exclusion of moisture. It was then distilled under reduced pressure and the middle fraction was collected over A.R. potassium hydroxide.

Tetrahydrofuran - The solvent was allowed to stand over anhydrous calcium chloride then fractionally distilled at atmospheric pressure. The distillate was refluxed over sodium wire for twenty - four hours. The solvent was stored in a dry box and re-distilled before use.

Glycollic Acid - Was supplied by Koch - Light Ltd.

Thionyl Chloride - was re-distilled at atmospheric pressure just before use (boiling point 76.5°C).

Silver Oxide - was supplied by B.D.H. Limited, heated in vacuum, drying for twenty hours at 100°C and stored in a dry box.

Phosgene - This was supplied by B.D.H. Laboratory Gas Service Ltd.

Thiophosgene - This was supplied by EGA - CHEMIE.

Decalin - was supplied by B.D.H. Ltd. The solvent was washed three times with dilute (7% w/v) sulphuric acid, once with dilute (10% w/v) sodium hydroxide and finally, three times with water. The washed material was dried over calcium sulphate, fractionally distilled under reduced pressure, the middle fraction, boiling at 63° C /6mm Hg pressure was collected and stored over sodium wire. The decalin was again redistilled immediately before use.

Dimethyl Sulphoxide (DMSO) - was shaken several times with anhydrous calcium sulphate and then refluxed over anhydrous barium oxide for twenty four hours. It was fractionally distilled under reduced pressure and collected over anhydrous barium oxide. The solvent was redistilled under reduced pressure prior to use.

Anisole - A.R. grade was allowed to stand over anhydrous calcium chloride for twenty-four hours followed by fractional distillation at reduced pressure on to anhydrous barium oxide. It was redistilled immediately before use.

α- hydroxy isobutyric acid -Supplied by Cambrian Chemicals.

∝- picoline - The material was refluxed over sodium hydroxide for twenty-four hours. It was fractionally distilled at atmospheric pressure, the middle fraction collected onto barium oxide.

2, 6-Lutidine - It was purified as ∝- picoline.

2-methoxy pyridine - Supplied by Koch - Light Lab. Ltd. and purified as ∝- picoline.

1,4-Dioxane - This was supplied by B.D.H. Ltd. It was shaken with calcium sulphate and allowed to stand overnight, then distilled from sodium and stored over fresh sodium wire. The middle fraction, B.Pt. 101° C/ 760 mm Hg was collected.

Chlorobenzene - This solvent was shaken several times with anhydrous calcium sulphate and fractionally distilled onto baked barium oxide at atmospheric pressure. It was redistilled prior to use, the constant boiling fraction at 132°C was collected.

Cyclohexanol - 1 - carboxylic Acid - This was obtained from Newton Maine Limited.

Tartronic acid - Supplied by Cambrian Chemicals, this was kept over P_2O_5 in a desiccator under vacuum for several days prior to use.

2.4 SYNTHESIS AND CHARACTERISATION OF COPPER (11) SALTS OF ∝- HYDROXY ACIDS

Copper (11) salts of ∝- hydroxy acids provide an alternative precursor to anhydrosulpite and anhydrocarboxylate preparation. It was used in some cases instead of the ∝-

hydroxy acids themselves.

Ammonium hydroxide was added to a slurry of the ∝-hydroxy acid (1.0 molar solutionin distilled water) until the solution became neutral (checked with pH paper) and the solution heated to boiling to remove any excess of ammonia. An equal volume of 0.5 molar copper (11) chloride solution to the ice -cooled, neutral solution of the aqueous ammonium salt until precipitation of the copper (11) salt of the ∝- hydroxy acid was complete. The salt was separated by filtration, washed with distilled water and diethyl ether and finally dried by heating at 100°C under vacuum for fifty hours. The absence of moisture was confirmed by T.G.A. and infra - red spectrometry.

Copper (11) salts, Figure (2.7) can be easily characterised by their infrared spectra. The free hydroxyl stretching

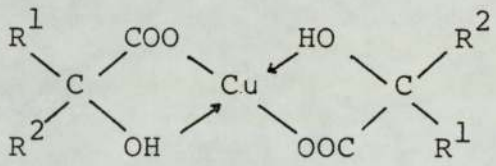


FIGURE (2.7)

absorption in the region of 3400 cm^{-1} shown by the free acid is displaced and changed in shape in the copper (11) salt. They are believed to be the hydroxyl groups that co-ordinate with the copper (11) metal. The carbonyl streching frequency at 1740 cm^{-1} in the acid is replaced by the carboxylate ion streching band which occurs at a lower wave number (approximately 1630 cm^{-1}).

Figure (2.8) shows the infrared absorption spectrum of copper (11) salt of glycollic acid.

Advantages of Using Copper (11) Salts Route

The use of copper (11) salt in the synthesis of anhydrosulphite and anhydrocarboxylate has several advantages over direct use of the α- hydroxy acids.

1. The reaction of phosgenewith α- hydroxy acids (equation 2.17) gives a quantity of α- chloro acid impurity, while attack of phosgene on the copper (11) salt (equation 2.16) leads mainly to acyl-chloroformate, which is changed to anhydrocarboxylate by eliminating hydrogen chloride.

2. Copper (11) salts are easy to prepare and may easily be obtained in an anhydrous state. Traces of moisture reconvert the monomers back to the parent acid and hence lower the yield for the reaction.

3. Chloride impurities are removed as the precipitate of anhydrous copper (11) chloride on filtering.

2.5 Synthesis and Purification of Anhydrocarboxylates of α- Hydroxy Carboxylic Acids

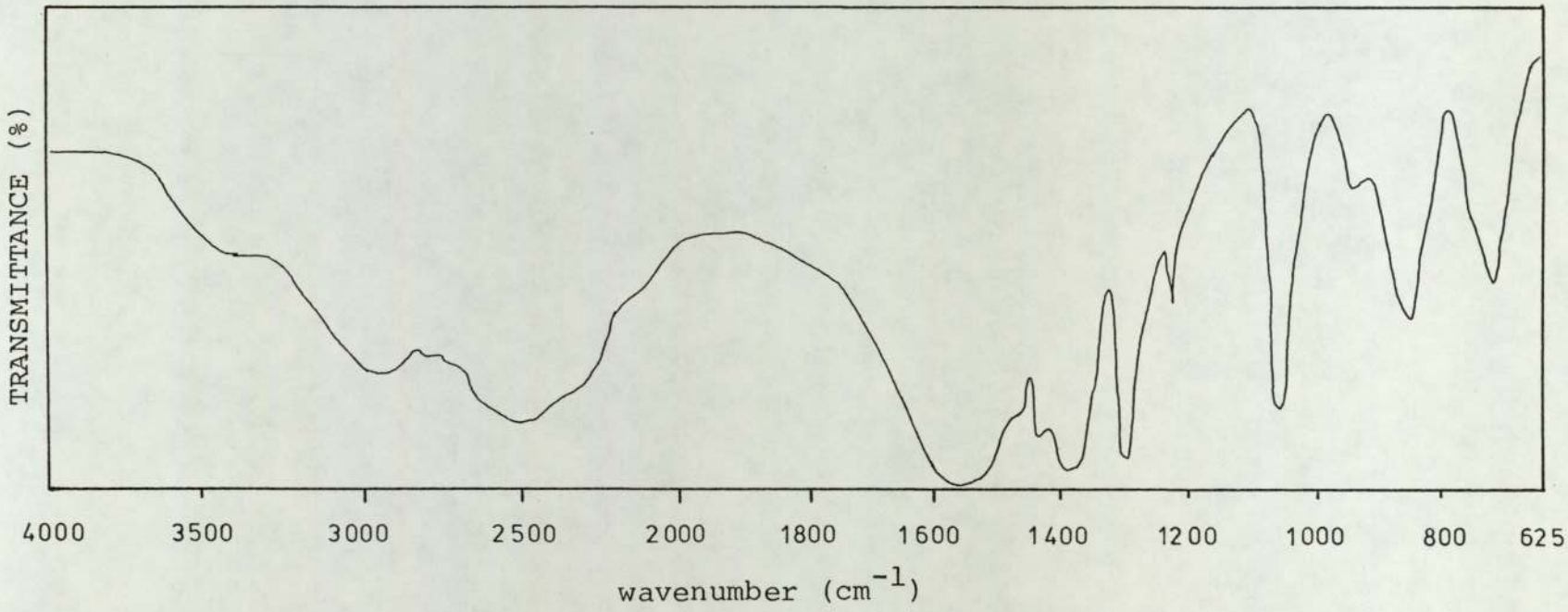
The anhydrocarboxylates of α- hydroxy acids may be prepared by using two routes:

(a) From phosgene and copper (11) salts of the α - hydroxy acid.

The anhydrous copper (11) salt (0.05 mole) was slurried in anhydrous ether (150 mls) and a solution of phosgene (0.1 moles)

Figure 2.8

Infra-red spectrum of copper (11)salt of glycollic acid. KBr disc, reference air.

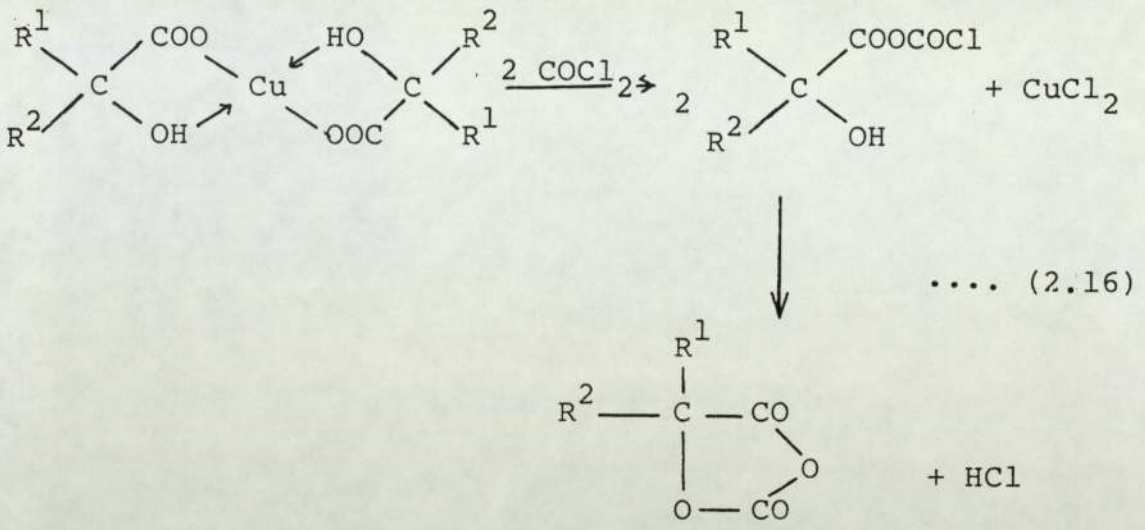


dissolved in anhydrous ether (75 mls) added, at 0°C. The reaction was stirred for four days at room temperature. The precipitate of copper (11) chloride was removed by filtration and washed with anhydrous ether to remove absorbed anhydrocarboxylate. The solvent, hydrogen chloride and any unreacted phosgene were removed at room temperature under vacuum (10 - 20 mm Hg). Finally the crude product was left under higher vacuum (0.5 - 1.0 mm Hg) for three hours to remove traces of volatiles.

(b) Action of Phosgene with ∝- hydroxy carboxylic acid

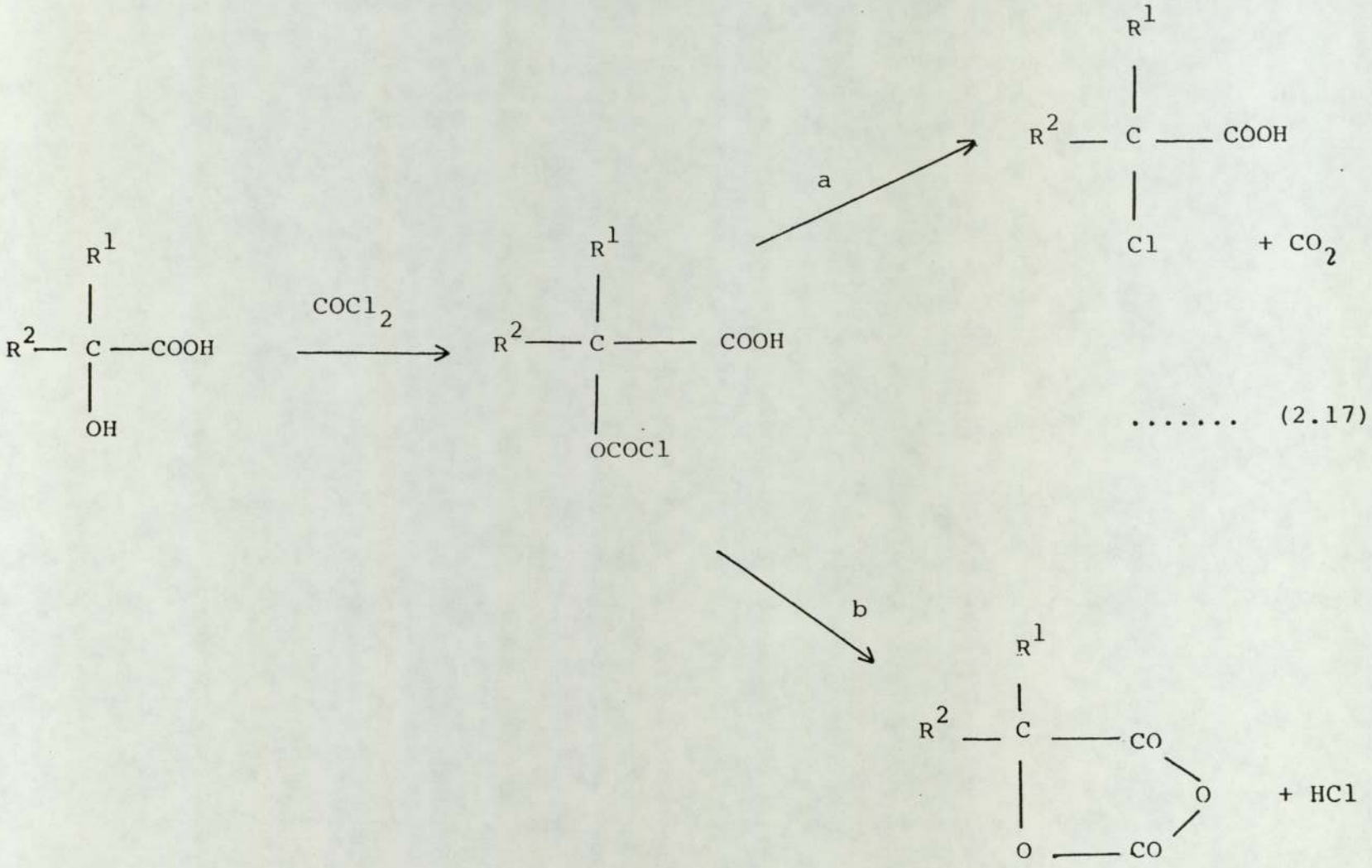
This method [19] involved the simultaneous addition of phosgene (0.25 mole) in 200 ml. of anhydrous ether and a solution of (0.33 moles) of pyridine in 200 ml. of dry ether to (0.16 mole) of ∝- hydroxy carboxylic acid in dry anhydrous ether. The reaction mixture was kept at (0 - 5°C) and constantly stirred for two hours. Precipitated pyridine hydrochloride which appeared immediately was then removed by filtration and washed with anhydrous ether to remove any anhydrocarboxylate remaining on the precipitate. The resultant solution was evacuated (using water pump) to remove excess ether, unreacted phosgene and hydrogen chloride. The solid remaining left under vacuum for 2 - 3 hours to remove the final traces of volatile material.

The reaction of phosgene with the copper (11) salt of ∝- hydroxy acid involves the formation of an acyl chloroformate by an attack of phosgene molecule at the carboxylate anion as shown overleaf.



.... (2.16)

This method of synthesis of anhydrocarboxylate of ∝ - hydroxy acid, had been chosen because of greater advantages over the other method in which ∝- hydroxy acids were directly reacted with phosgene (2.5 b). The reaction of phosgene with ∝ - hydroxy acids gives an appreciable quantity of ∝- chloro acid impurity, as shown by a suggested reaction scheme over the page. The alkyl chloroformate, addition product of phosgene on the hydroxyl terminal of an ∝- hydroxy acid, tends to lose carbon dioxide to form the ∝ - chloro acid by an SN_i type reaction. The loss of hydrogen chloride from the chloroformate results in cyclisation to give an anhydrocarboxylate ring. Pyridine was used to assist the cyclisation of the alkyl chloroformate (step b equation 2.17) by the elimination of hydrogen chloride to form pyridine hydrochloride. The amount of pyridine must be


R1
R2 — C — COOH
OH
COCl2
R1
R2 — C — COOH
OCOCl
a
R1
R2 — C — COOH
Cl
+ CO2
b
R1
R2 — C — CO
O
O — CO
+ HCl

..... (2.17)

controlled as it is used as initiator in the present work and the excess of pyridine may help the decomposition of pre-formed anhydrocarboxylate.

The removal of hydrogen chloride by pyridine has been discussed in the reaction of alcohols with phosphorus trichloride[99] and in the decomposition of alkyl chloroformates[100].

Purification

It is known that the impure anhydrocarboxylate contains chlorine derivative impurities (Equations 2.16, 2.17) play an important role in polymerisation, so that it was necessary to estimate the chlorine ion concentration in the monomer in order to purify them before carrying out the polymerisation reactions. For this purpose potentiometric method which described in section(2.1)was used. The crude product was redissolved in an excess of anhydrous ether and stirred for 15 hours with a two mole excess of baked silver oxide based on chloride content. The silver chloride and the unreacted silver oxide were then removed by filtration and the ether stripped off. The resulting anhydrocarboxylate contained no chlorine as detected by the potentiometric method. The chlorine free anhydrocarboxylate was finally purified by vacuum sublimation (section 2.2). For the anhydrocarboxylates which were prepared, suitable conditions for vacuum sublimation were found to be as shown below:

Monomer	Crude Anhydrocarboxylate	Cold Finger	Pressure mm Hg
DMAC	34 - 36°C	Dry ice	0.5 - 1.0
GAAC	10 - 14°C	0 - 5°C	0.5 - 1.0

2.6 SYNTHESIS AND PURIFICATION OF ANHYDROSULPHITES OF α - HYDROXY ACIDS

The anhydrosulphites of α- hydroxy acids were prepared by using two methods[66] : the action of thionyl chloride on

(a) the dry α- hydroxy acid and

(b) the anhydrous copper (11) salt of α - hydroxy acid.

(a) Route Via the α- hydroxy acid

Redistilled thionyl chloride (1.5 mole) in 200 ml of anhydrous ether was added slowly to a stirred solution of the α- hydroxy acid (1.0 mole) in anhydrous ether (400 ml) at (- 5°C). The reaction mixture was allowed to warm to room temperature and then stirred for 20 hours. Ether was then slowly removed under partial vacuum at 15 - 20°C., finally residual ether and thionyl chloride were removed under reduced pressure (1.0 - 5.0 mm Hg).

(b) Route Via the copper (11) salt of the α - hydroxy acid

The dry anhydrous copper salt (1.0 mole) was slurried in 500 ml. anhydrous ether at 0 - 5°C. Redistilled thionyl chloride (1.5 mole) in 200 ml anhydrous ether was then added dropwise over two hours. The resulting precipitate of copper chloride was then filtered off and washed with anhydrous ether to remove any anhydrosulphite. The filtrate was then left for one hour under reduced pressure (10 - 15 mm Hg) at room temperature and final traces of thionyl chloride were evaporated under vacuum as in (a).

It has been suggested that the mechanism involved in the formation of α- hydroxy acid anhydrosulphite by first route (a) is that the α- hydroxy carboxylic acid reacts with

thionyl chloride to form initially, an alkyl chlorosulphinate (Figure 2. 9 A) as an intermediate. This chlorosulphinate may then react intramolecularly with the carboxylic acid group of the same molecule to yield an anhydrosulphite (B) by elimination of hydrogen chloride (Figure 2. 9 a). Alternatively the alkyl chlorosulphinate may lose sulphur dioxide with the formation of an alkyl chlorine compound (C) by an SN_i type reaction or there may be further attack by thionyl chloride on the carboxylic acid group to yield, finally, an acyl chloride. From the last two reactions which may take place, α - chloro acid chloride (D) is the main product, which has been shown[101] to be the major impurity in the preparation of most of the anhydrosulphites synthesised.

Reaction of thionyl chloride with the copper (11) salt of α- hydroxy acid has been shown to have several advantages over direct use of the acid itself. In addition to that advantages which were mentioned in section 2.4, the mechanism of reaction between thionyl chloride and copper (11) salt of α - hydroxy acid differs from that of the parent acid and thionyl chloride. It has been suggested that thionyl chloride attacks the carboxylate anion rather than the hydroxylic group of the copper salt, with the product intermediate being an acyl chlorosulphinate (A , Equation 2 - 18). Anhydrosulphite (B) is formed by loss of hydrogen chloride from the acyl chlorosulphinate.

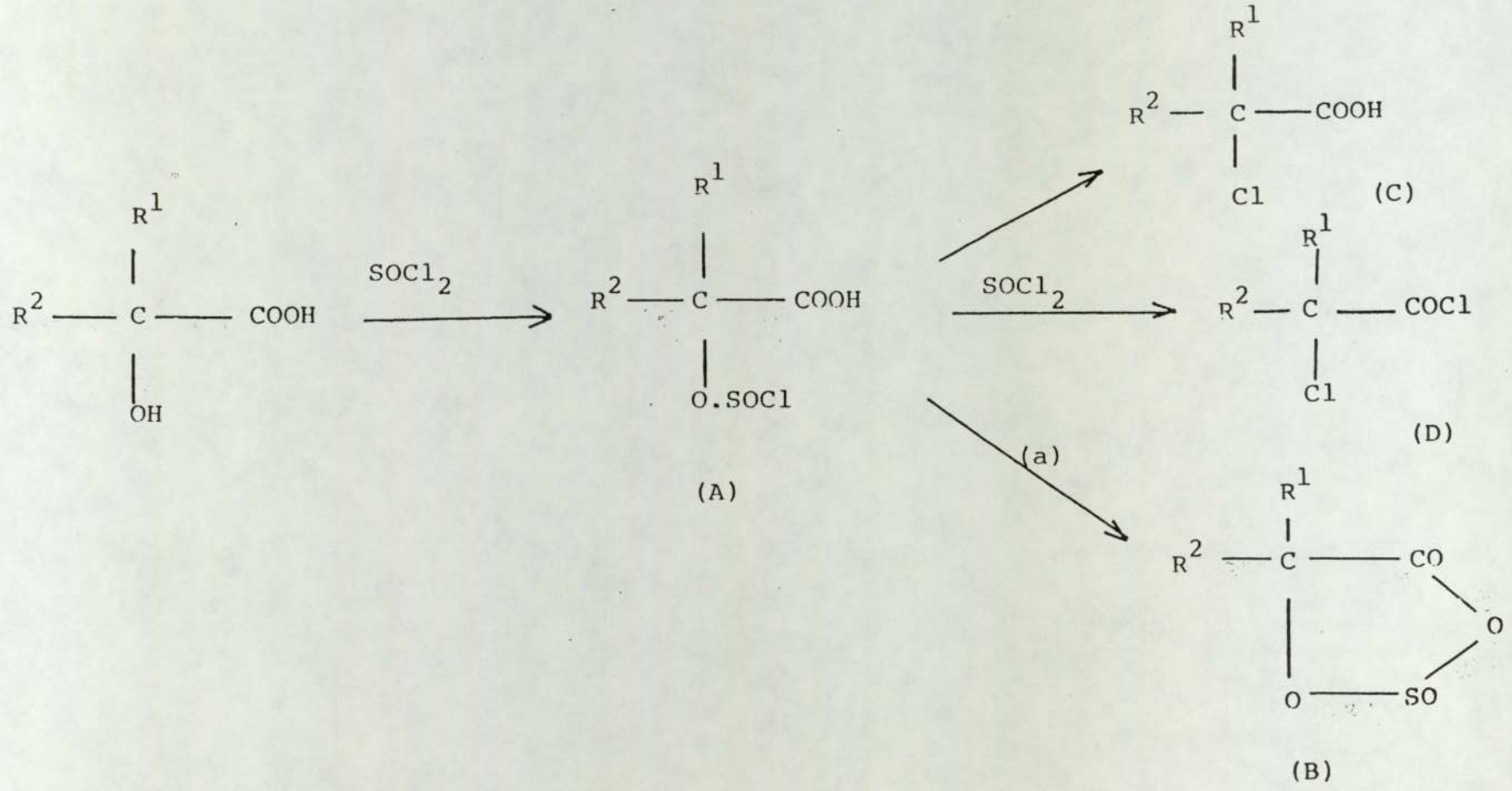
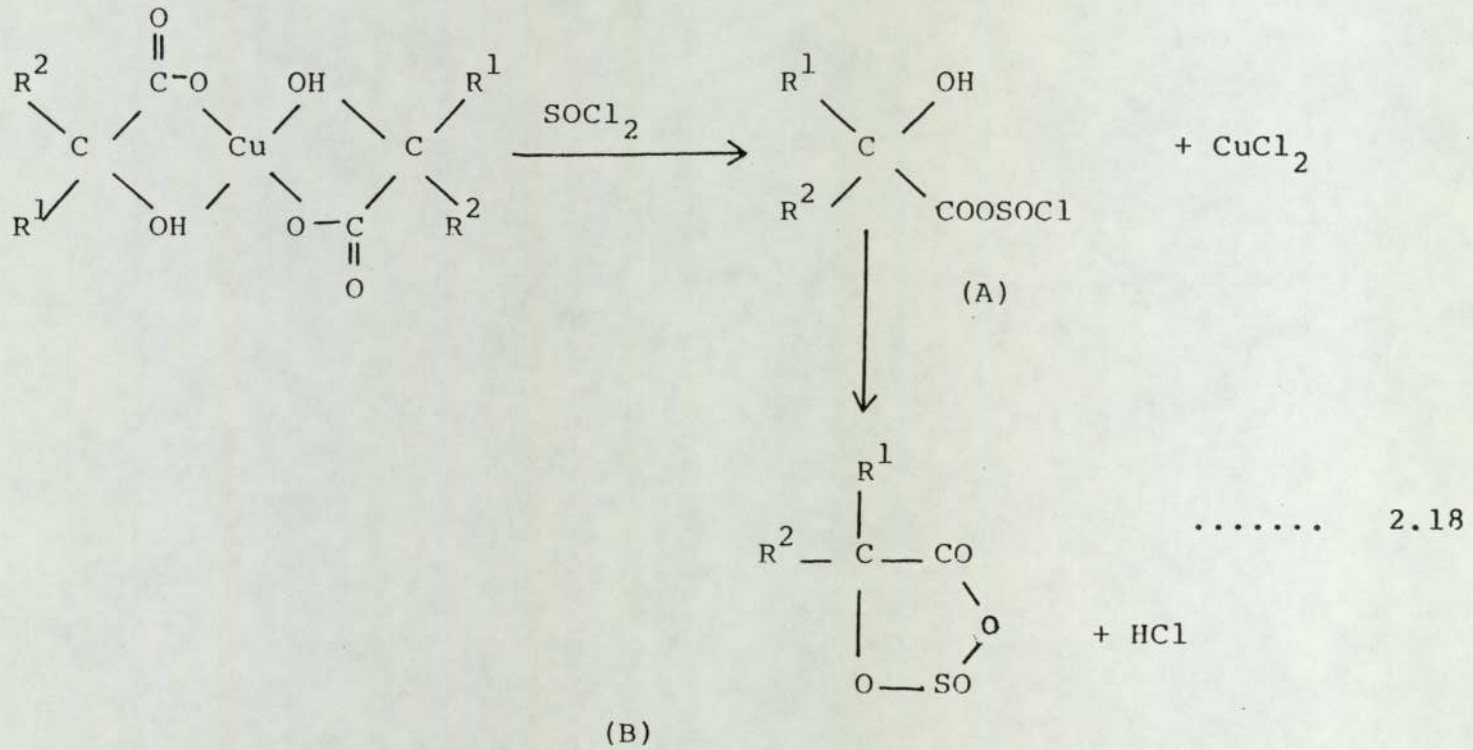


Figure (2.9) Reaction of thionyl chloride with α - hydroxy acid



..... 2.18

Since an acyl chlorosulphinate (Equation 2.18) is expected to be rather more stable than an alkyl chlorosulphinate (Figure 2.9), the former is less likely to lose sulphur dioxide with the formation of chlorine containing impurities. The probability of formation of acid chloride or α- chloro acid chloride is therefore, much reduced.

Purification

It has been shown that in almost every anhydrosulphite synthesis the major impurities are chlorine containing compounds having either acyl or alkyl chlorine, and the parent α - hydroxy acid resulting from unreacted starting material or from the ingress of trace moisture. The total ionisable chlorine in the impure anhydrosulphite was determined by potentiometric titration as described in section 2.1. Thomas [62] has concluded that the most rapid and efficient removal of chlorinated impurities is brought about by silver oxide and thus this was used to purify the anhydrosulphites.

A two molar excess of silver oxide (based on chlorine containing impurity) as a slurry in anhydrous diethyl ether, was added to the impure anhydrosulphite contained in the conical flask. The mixture was agitated with a magnetic stirrer and maintained at 0 - 5^{o}C by means of an ice-bath. After four hours the residue was removed by filtration and ether removed under vacuum. The anhydrosulphite thus obtained was fractionally distilled to remove the parent acid impurity. The purified anhydrosulphites were stored in a refrigerator until needed for kinetic studies.

2.7 Characterisation of anhydrocarboxylates and anhydrosulphites of α- hydroxy acid

The structures of the ring compounds prepared from α - hydroxy acids, anhydrocarboxylates and anhydrosulphites are shown in Table (2.1). The groups R^1 and R^2 are those attached at the C - 5 position. These ring compounds may be named systematically, however for the convenience of the reference throughout the text, the trivial names or their abbreviations make the ring compound easily identified.

The anhydrocarboxylates and anhydrosulphites of α- hydroxy carboxylic acid were characterised by various instrumental techniques. Infra - red spectroscopy was used to characterise the anhydrocarboxylate and anhydrosulphites and the spectra are shown in Figures (2.10) and (2.11) respectively. The infra - red spectra of the anhydrocarboxylate display greater changes from the parent α- hydroxy acid in both hydroxyl and carbonyl absorption regions. Anhydrocarboxylates show two stretching frequencies in the carbonyl region and no hydroxyl stretching in the 3400 cm^{-1} wave-number range. These two bands represent the stretching vibrations of the two carbonyl groups in the anhydrocarboxylate ring (IX) due to the different environments. The higher frequency band ($\nu_{c=o}$ = 1890 $\pm$ 10 cm^{-1}) being of medium strength when compared to the lower frequency stretching ($\nu_{c=o}$ =1810 $\pm$ 5 cm^{-1}) which is of high intensity. The position of these stretching frequency values are at higher frequencies than those a single peak of their parent acids ($\nu_{c=o}$ 1720 $\pm$ 5 cm^{-1}). This may be explained on the basis of ring strain of the anhydrocarboxylate ring in which these two carbonyl groups are situated. Figure (2.12)

TABLE 2.1

α - Hydroxy acids and their anhydrocarboxylates and anhydrosulphites

ANHYDROCARBOXYLATES and ANHYDROSULPHITES (Systematic name)	ABBREVIATION	R_1	R_2	PARENT ACID	METHOD OF PREPARATION	m.p. or b.p. (°C)
5,5 - dimethyl - 1, 3 - dioxlan -2, 4 - dione	DMAC	CH_3	CH_3	1-hydroxy isobutyric acid	2.5 b	39 - 40
1,3 - dioxolan - 2, 4 - dione	GAAC	H	H	Glycollic acid	2.5 a	18
5,5 - dimethyl - 1,3 2-dioxathiolan - 4 - one - 2 - oxide	HBAS	CH_3	CH_3	1-hydroxy isobutyric acid	2.6 a	56 - 57 at 12 mm
Cyclohexane spiro - 5 - 1,3,2 - dioxathiolan - 4 - one -2- oxide	C′ hex AS	$(CH_2)_5$		Cyclohexanol -1 carboxy -lic acid	2.6 a	68 - 70 at 0.5mm
1,3,2-dioxathiolan 4 - one - 2 - oxide	GAAS	H	H	Glycollic Acid	2.6 b	68 - 70 at 12mm
5- carboxyl- 1,3,2 dioxathiolan -4-one - 2 - oxide	TAAS	H	COOH	Tartronic Acid	2.6 a	—

Figure 2.10

Infra-red spectrum of DMAC . The spectrum was recorded as a thin film using KBr plates, the reference cell was air.

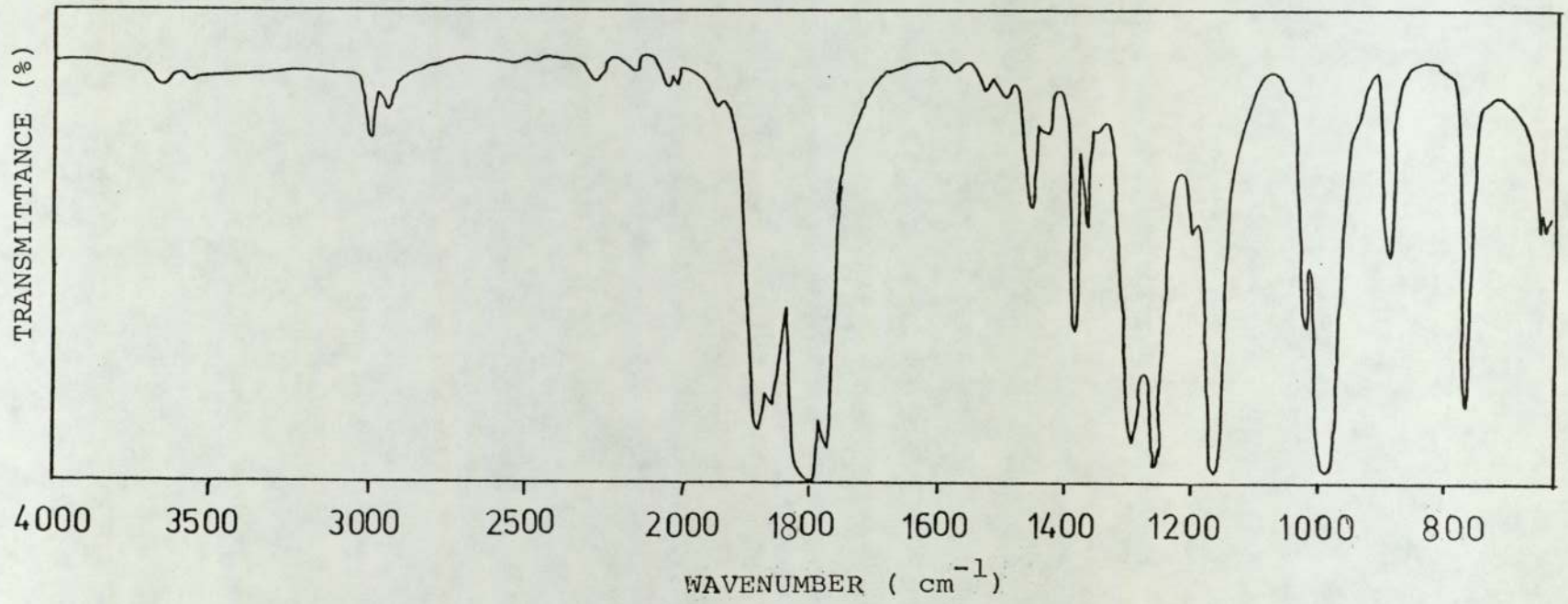
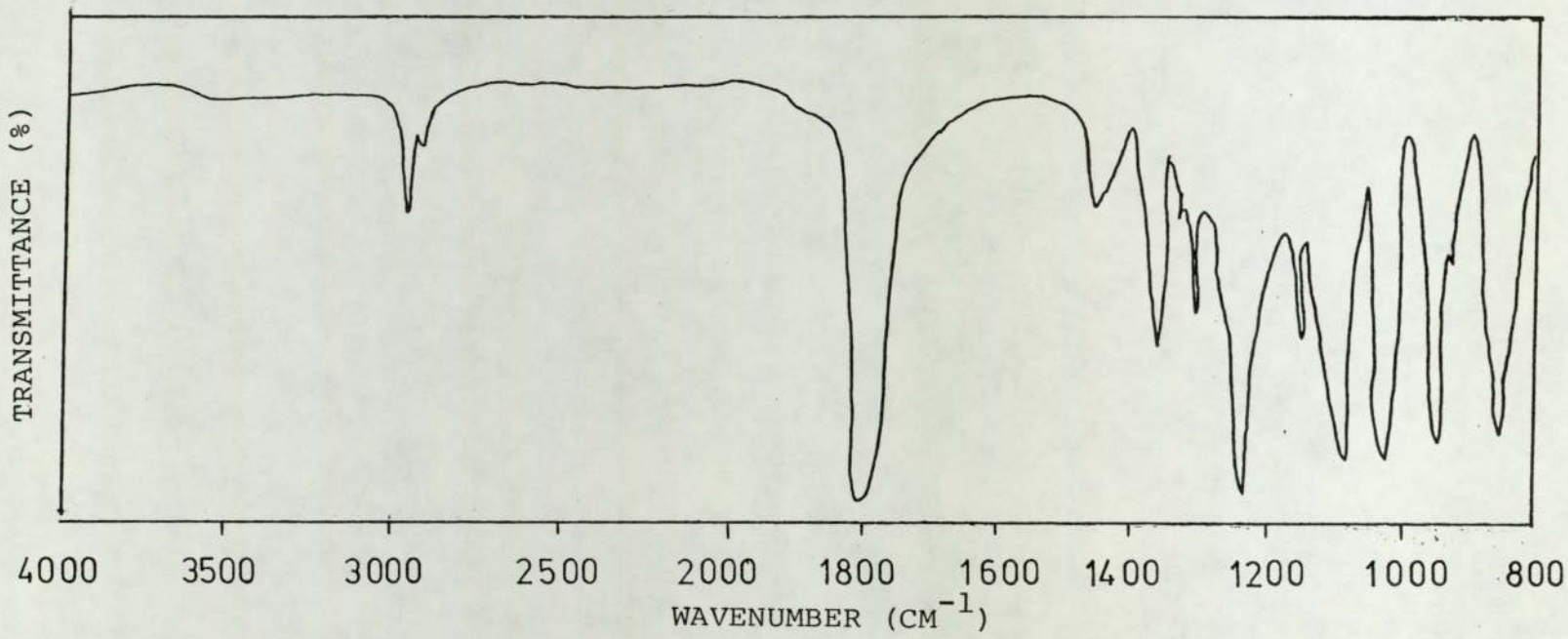


Figure 2.11

Infra-red spectrum of HAAS . The spectrum was recorded as a thin film using KBr plates, the reference cell was air.



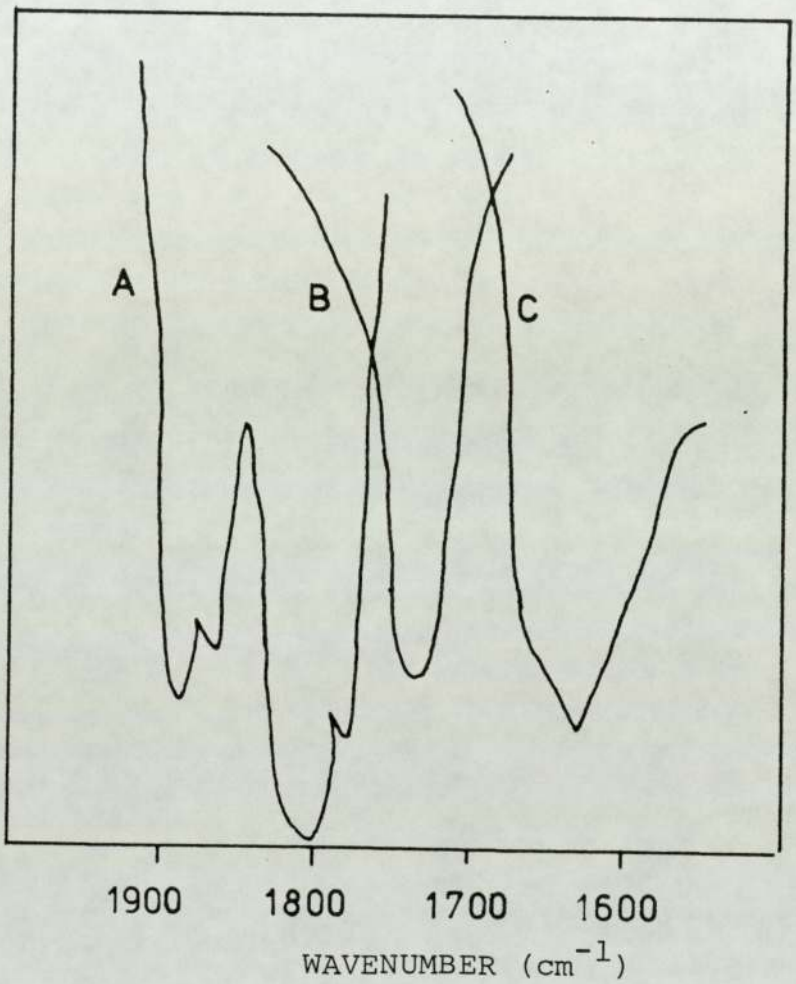


Figure 2.12

Change in characteristic carbonyl absorption frequency

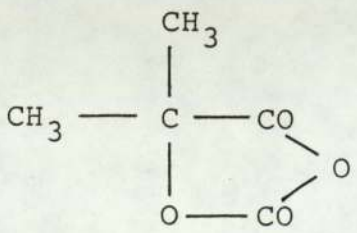
A : Anhydrocarboxylate

B : ∝ - Hydroxy acid

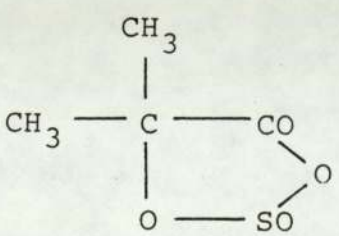
C : Cupric salt of the acid

shows a typical change in carbonyl frequency during the progressive synthetic steps from ∝ - hydroxy acid ($\nu_{c=o}$ = 1740 cm^{-1} to copper (11) salt ($\nu_{c=o}$ 1620cm^{-1}) and finally to the anhydrocarboxylate. The anhydrosulphite (Figure 2.11) gives a single absorption in the carbonyl region. The frequency of this absorption at 1815 $\pm$ 10 cm^{-1} is higher than those of their parent acid. The sulphoxide stretching frequency is found at 1240 cm^{-1} as a medium intensity peak. Table (2.2) shows some physical properties of anhydrocarboxylates and anhydrosulphites.

Further confirmation of anhydrocarboxylates and anhydrosulphites can be provided by n.m.r. and mass spectral analysis. The chemical shifts from high resolution nuclear magnetic resonance carried out in 5 - 10% w /v solution of ∝ - hydroxy acid anhydrocarboxylate and anhydrosulphite in deuterated chloroform are shown in table (2.3).
The different proton resonance between anhydrocarboxylate and anhydrosulphites is related to the structure of these compounds. As anhydrosulphite ring is puckered and anhydrocarboxylate is planar ring so there is the possibility of two configurations in the anhydrosulphite which results in two chemically equivalent substituents at C(5) becoming magnetically non - equivalent. This is explained well in dimethyl anhydrocarboxylate (DMAC) and dimethyl anhydrosulphite (HBAS)



DMAC



HBAS

TABLE 2.2

Physical properties of a series of anhydrocarboxylates and anhydrosulphites

Anhyrdocarboxylate	Anhydrosulphites	Yields %	Gas evolved % theoretical		Infra- red spectra	
			SO_2	CO_2	$\nu_{c=o}$ (cm-1)	$\nu_{s=o}$ (cm-1)
GAAC		50		98 ± 2	1810(S) 1890(M)	–
DMAC		62		97 ± 2	1815(S) 1890(M)	–
	GAAS	45	98 ± 2		1825(S)	1245(M)
	HBAS	72	98 ± 2		1810(S)	1240(M)
	Chex AS	64	97 ± 2		1810(S)	1238(M)
	TAAS	57	95 ± 2		1830(M) a 1750(S) b	1225 (W)

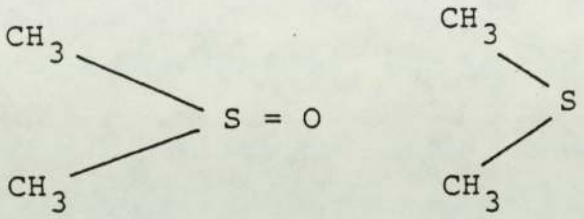
S = strong
M = medium
W = weak

TABLE (2.3)

Nuclear magnetic resonance spectra recorded as deuterochloroform Solutions, 10% W/V at 100 MHz. Reference T.M.S.

PARENT ACID			∝ - hydroxy acid	Anhydrocarboxylates	Anhydro-sulphites
	R_1	R_2			
1 - hydroxy isobutyric acid	CH_3	CH_3	8.52 τ	8.28τ	8.25τ 8.41τ
Glycollic acid	H	H	6.05 τ		4.76τ 5.17τ
Cyclohexanol - 1 - Carboxylic acid	$(CH_2)_5$		8.27 τ 3.00 τ		8.21τ

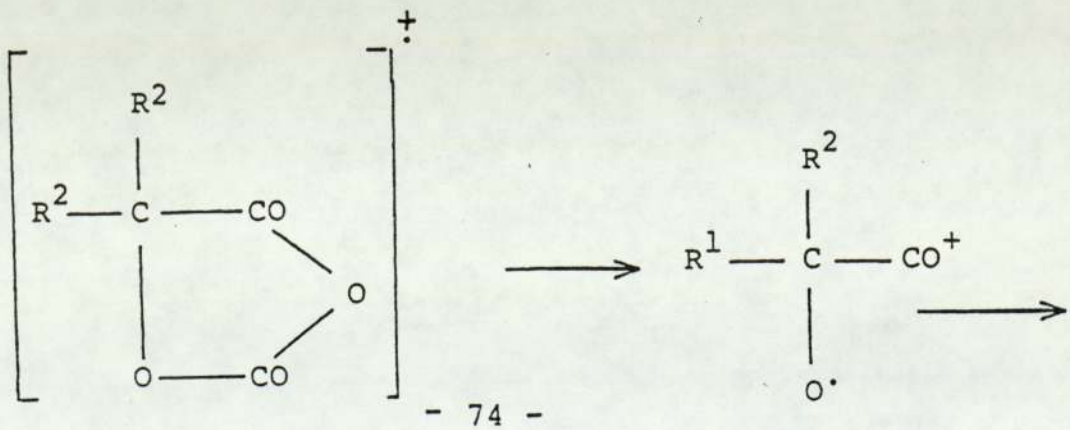
The n.m.r. spectrum has been resolved in terms of the two postulated ring sulphur configurations which produces two peaks of equal intensity in case of HBAS due to the effect of sulphoxide group on the methyl groups. The effect of sulphoxide group (S = O) on the proton resonance was studied[102] by using dimethyl sulphoxide (A) and dimethyl sulfide (B) and found

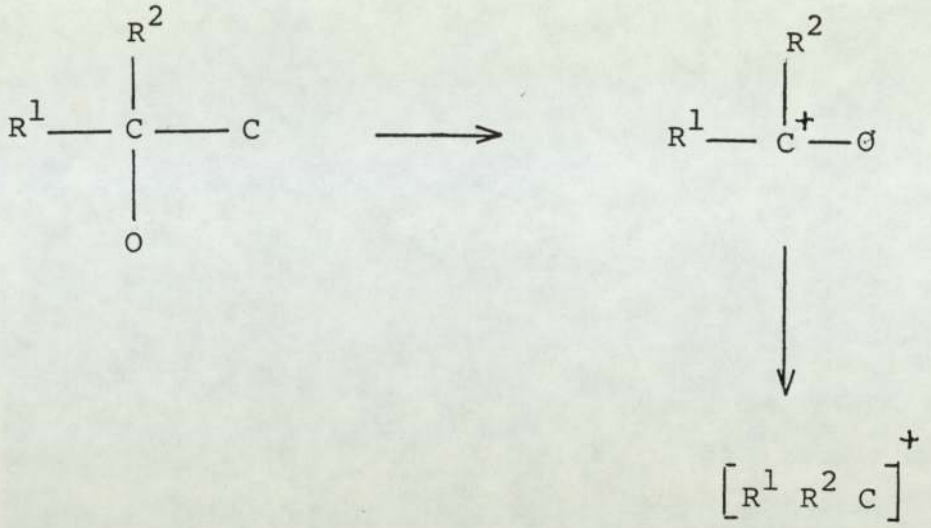


(A) (B)

that there is a difference between the chemical shifts of the methyl groups in dimethyl sulphoxide (τ = 7.62 p.p.m) and dimethyl sulphide (τ =8.00 p.p.m.), due to the electronic effect of the S = O group which shifts the methyl peak.

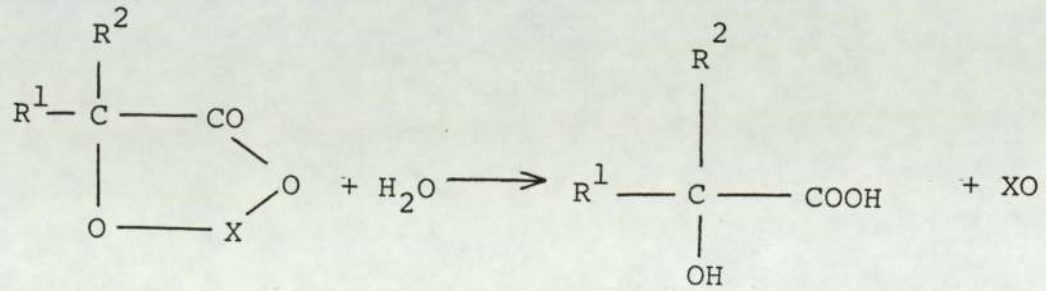
The mass spectra of anhydrocarboxylates has been studied and it is interesting to note that the top mass peaks observed corresponding to the molecular weight of the anhydrocarboxylate. Principal ring fragmentation peaks are observed at (M - 44), (M - 60), (M -72) and (M - 88) which corresponds to the following fragmentation scheme:





This is contrast to anhydrosulphites which do not give the molecular ion peak in their mass spectra, indicating their relatively lower thermal stability when compared to anhydrocarboxylates.

Elemental analysis of anhydrocarboxylates and anhydrosulphites are difficult to obtain because of their sensitivity to atmospheric moisture. Anhydrocarboxylates and anhydrosulphites of ∝- hydroxy acids studied reacted rapidly with water to yield the parent acids therefore quantitative



[X = CO or SO]

conversion on hydrolysis to the parent acid together with the volume of carbon dioxide or sulphur dioxide evolved as measured by manometery does provide a useful indication of their purity.

CHAPTER 3

Tertiary Base Initiated Polymerisation of 5,5 Dimethyl -1,3 - Dioxolan - 2,4 - Dione (DMAC)

None of the generally available methods for the polymerisation of five - membered cyclic derivatives of α - hydroxy carboxylic acids is without disadvantage. Thus both the thermal and hydroxyl initiated routes have limitations. Thermal polymerisation, for example, which is particularly useful in the case of disubstituted 1,3,2 - dioxathiolan - 4 - one - 2 - oxides (VIII), has only limited use with the more thermally stable 1,3- dioxolan - 2,4 - diones (IX).

Hydroxyl initiated polymerisation of these monomers is relatively slow and markedly affected by steric hindrance, these factors have been discussed in chapter 1. One particular problem that results from the limitations of hydroxyl initiated and thermal polymerisation is that the copolymerisation of unsubstituted or monosubstituted, monomers with disubstituted, is not feasible because of their very different reactivity. For biomedical application copolymerisations involving derivatives of tartronic acid, glycollic acid, and α - hydroxy isobutyric acid, would be of potential value.

In this chapter the polymerisability of dimethyl anhydrocarboxylate, DMAC, using tertiary base initiators of the heteroaromatic type, namely pyridine and its derivatives, has been examined in an attempt to find agents which are able to bring about ring-opening and polymerisation at reasonable rates and low temperatures.

It is known that the anhydrocarboxylates of α- hydroxy acids undergo polymerisation when treated with pyridine. It has been shown [89] that the presence of the bulky phenyl substituents at the C - 5 carbon to some extent sterically hinders the attack by the pyridine molecule, but in addition has an activating effect due to electron withdrawal. The effect of two alkyl substituents, which should offer some steric hindrance but not activate the ring, has not been previously studied. The results of this study are presented in this chapter.

3.1 Results

3.1.1 Pyridine Initiated Decomposition of DMAC in Nitrobenzene

The tertiary base initiated decomposition of DMAC was carried out in carefully dried nitrobenzene as reaction medium and the rate of decomposition measured by gas evolution kinetic technique. The low temperature kinetic apparatus described in chapter 2, shown in Figure (2.3), was used. The rise in pressure in the manometer due to the evolution of carbon dioxide was measured, with suitable intervals of time, which by Equation (2.7) enables the rate of disappearance of monomer to be followed.

3.1.2 Kinetic Profile and Effect of Temperatures

The reaction was carried out at various temperatures in the range 30 to 60° C, to enable the various activation parameters to be determined. A typical pressure against time is shown in Figure (3.1) which shows that the rate increases with increase in temperature. The corresponding semilog

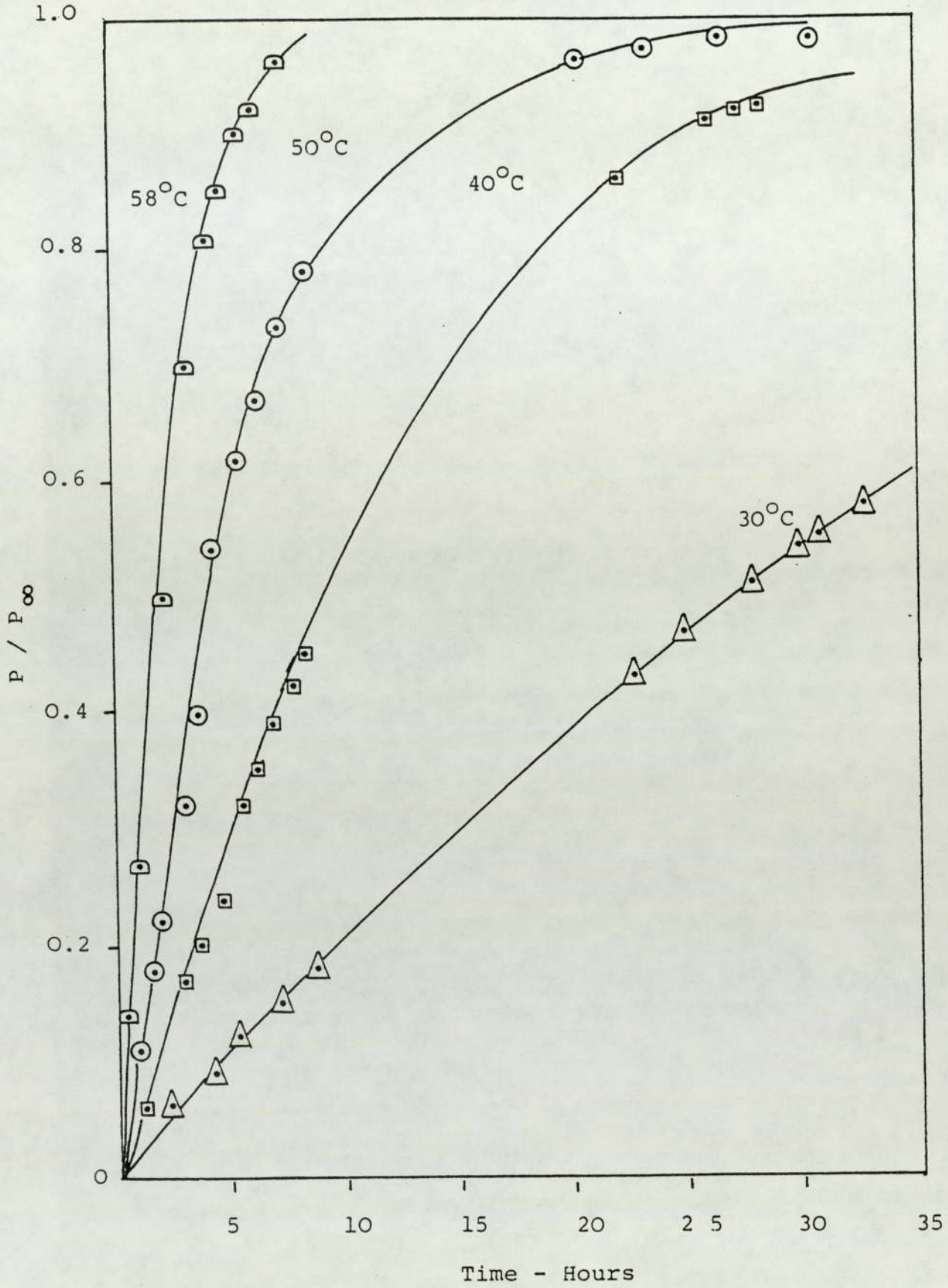


Figure 3.1 Initial rate curves for the decomposition of DMAC with pyridine at different temperature

$[M]_o$ = 0.427 mol. l^{-1} $[PY]$ = 0.38 mol. l^{-1}

plot(log $[(P_\infty - Pt) / P_\infty]$ versus time) which is shown in Figure (3.2) illustrates the first order dependence on monomer concentration and implies that the pyridine concentration remains constant through out the reaction. A more detailed presentation of the effect of initial pyridine concentration on the rate of reaction, and reaction products, is presented in a later section (3.1.3 , 3.1.5). For these initial studies the initial pyridine concentration was kept constant and almost equimolar concentrations of monomer and pyridine were used. In this concentration region the rate of monomer decomposition showed first order dependence on initial pyridine concentration. This behaviour is identical with that shown with similar monomers[90] and the mechanism deduced there is now examined as a basis for interpretation for these results . Under these conditions the rate of decomposition of DMAC in the presence of pyridine may in general be expressed by

$$-\frac{d[M]}{dt} = \frac{d[CO_2]}{dt} = k_2[M][PY] \quad \ldots 3.1$$

where $[M]$, $[PY]$ and k_2 are the concentration of DMAC, pyridine and second - order rate constant respectively. As the pyridine concentration is assumed to be constant during the course of the reaction, Equation (3.1) may be written as,

$$-\frac{d[M]}{dt} = k_1[M] \quad \ldots\ldots 3.2$$

Where $k_1 = k_2[PY]$

and can be considered as a pseudo first - order rate constant.

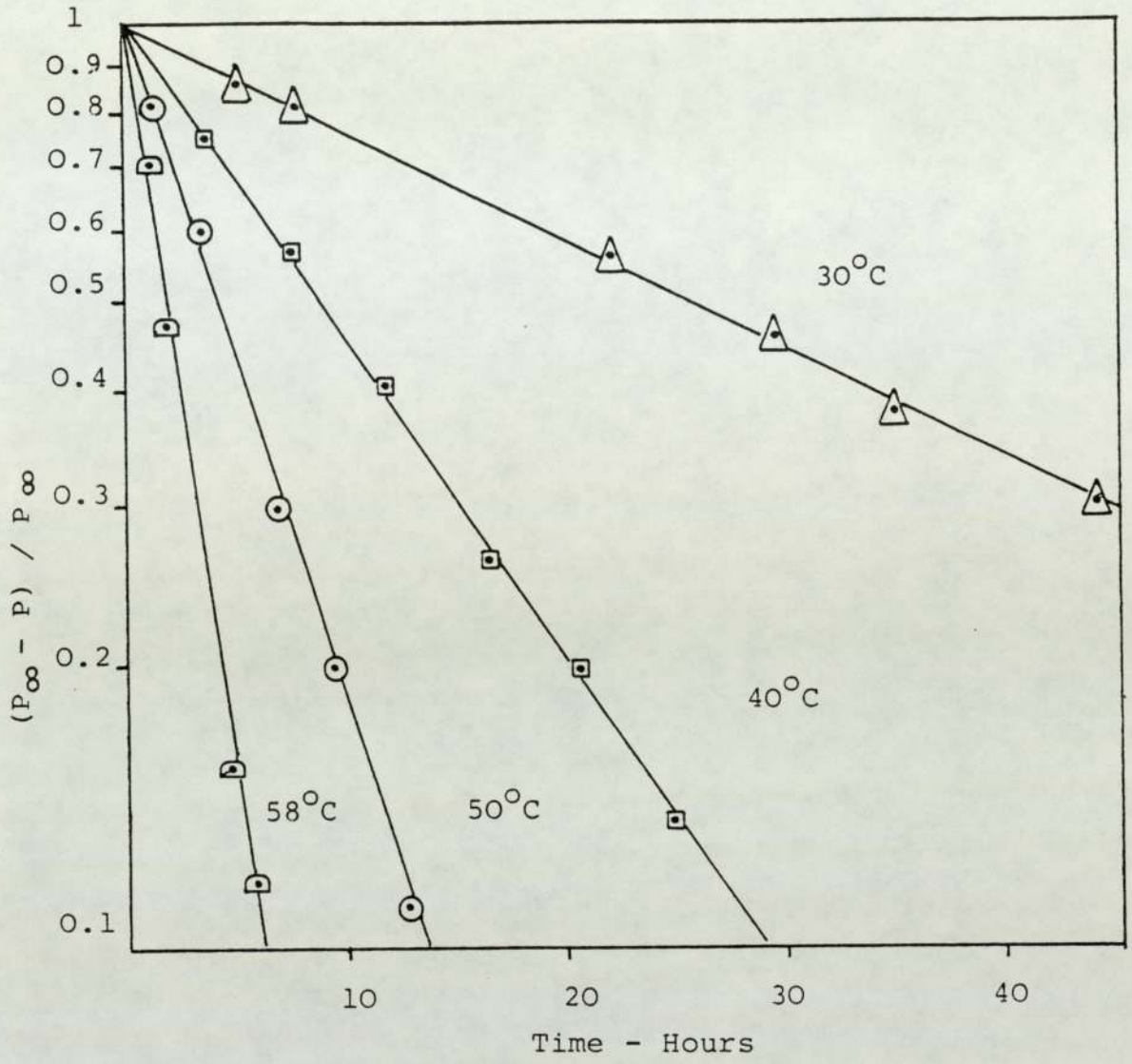


Figure 3.2 Semi-logarithmic plots of $(P_\infty - P) / P_\infty$ versus time for the decomposition of DMAC with pyridine in nitrobenzene at different temperature.

From Figure (3.2), the pseudo first order (k_1) and derived second order (k_2), rate constants can be calculated and are shown in table 3.1. Table (3.1) also shows the activation energy (E_a), pre - exponential factor (A) and entropy of activation ($\Delta S^{\ddagger}$) derived from a conventional Arrhenius plot (Figure 3.3). The magnitude of the activation energy is somewhat higher than the value expected for nucleophilic attack at an activated site, and the values for (A) and the entropy of activation would suggest that the formation of the transition state requires a specific orientation of the reactants.

Table 3.1

First order rate constant (k_1), second - order rate constant (k_2), energy of activation (E_a), pre - exponential factor (A) and entropy of activation ($\Delta S^{\ddagger}$) for the pyridine initiated polymerisation of DMAC in nitrobenzene.

$[DMAC]_o$ = 0.42 mol. litre^{-1}

$[PY]_o$ = 0.38 mol. litre^{-1}

Temperature ^{o}C	$10^5 k_1$ Sec^{-1}	$10^5 k_2$ l. mol.$^{-1}$ Sec.$^{-1}$
30	0.75	1.99
40	2.2	3.78
50	4.8	12.6
58	9.6	25.3

E_a	(k.J. mol.$^{-1}$)	82.6
A	(l. mol.$^{-1}$ Sec.$^{-1}$)	5.8 x 10^8
$\Delta S^{\ddagger}$	(J.K^{-1} mol.$^{-1}$)	- 76.9

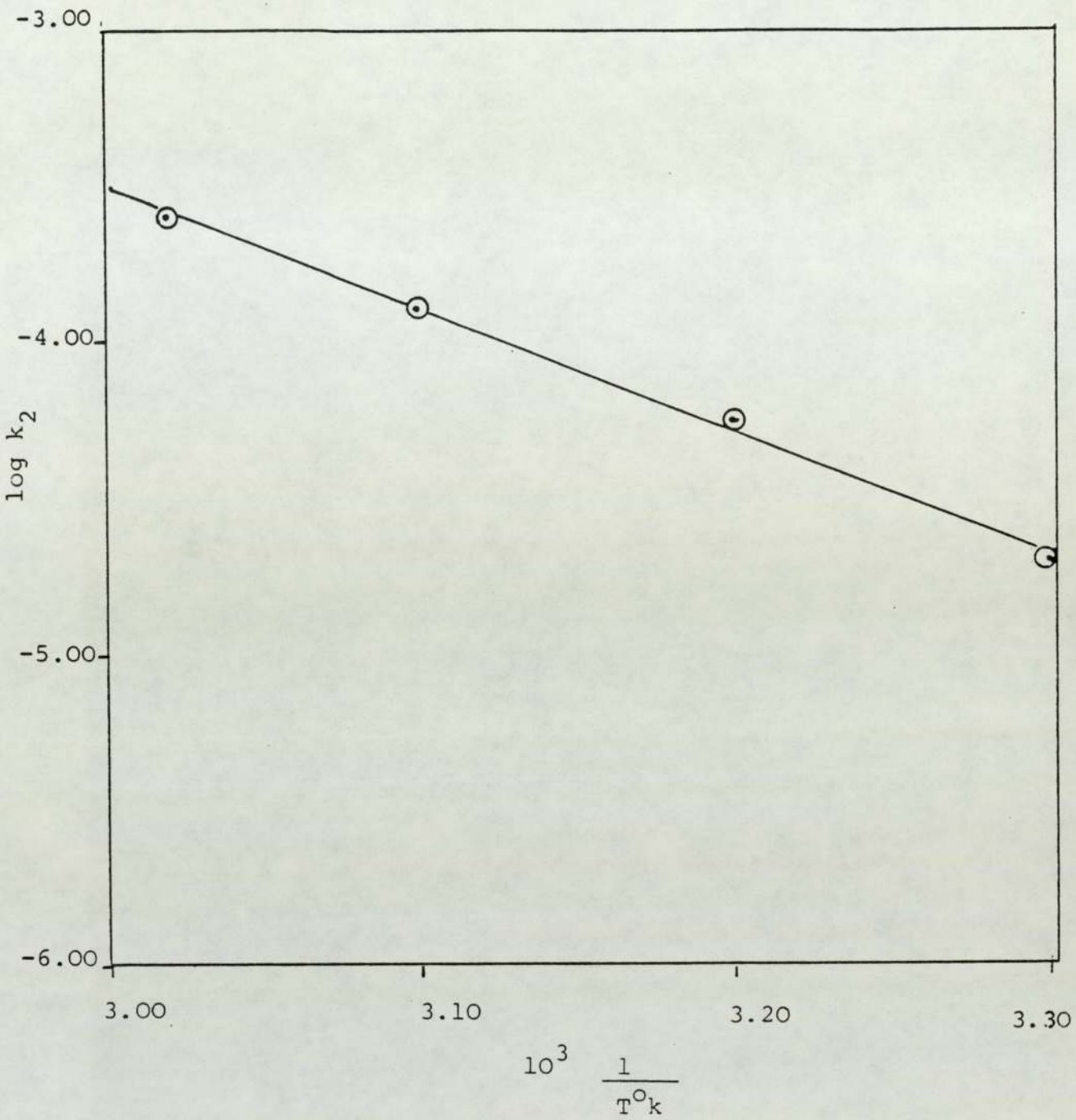


Figure 3.3 An Arrhenius plot of the second - order rate constant, log k_2, versus the reciprocal of the absolute temperature for the decomposition of DMAC with pyridine in nitrobenzene.
Temperature range 30 - 60°C.

3.1.3 Effect of Pyridine Concentration

The initial concentration of pyridine itself was one of the factors examined in order to obtain more information concerning the mechanism of this reaction. Figure (3.4) shows the initial rates for the decomposition of DMAC with different concentrations of pyridine. This shows that the increase in initial concentration of pyridine resulted in a corresponding increase in the rate of reaction. First-order (semi-logarithmic) plots (Figure 3.5) showed a linear dependence on residual monomer concentration even when substochiometric amounts of pyridine were used. Typical results for the decomposition of DMAC with various concentrations of pyridine at 59^{o}C are listed in Table (3.2) in which the values of first - order rate constants (Equation 3.2) are given. Figure (3.6) demonstrates that monomer decomposition showed a first - order dependence upon the initial concentration of pyridine especially when substoichiometric amounts of pyridine were used. The overall decomposition may, therefore, be expressed in the form of Equation (3.1). Higher concentrations of pyridine begin to modify the nature of the reaction medium and are difficult to interpret.

3.1.4. Effect of Varying the Structure of Substituted Pyridines

A series of substituted pyridines were used in the decomposition of DMAC in order to get more information concerning the nature of pyridine initiation and the relative rates of attack of tertiary bases varying in basicity and steric availability of the nitrogen atom. The nucleophilicity of the nitrogen in pyridine may be increased by the

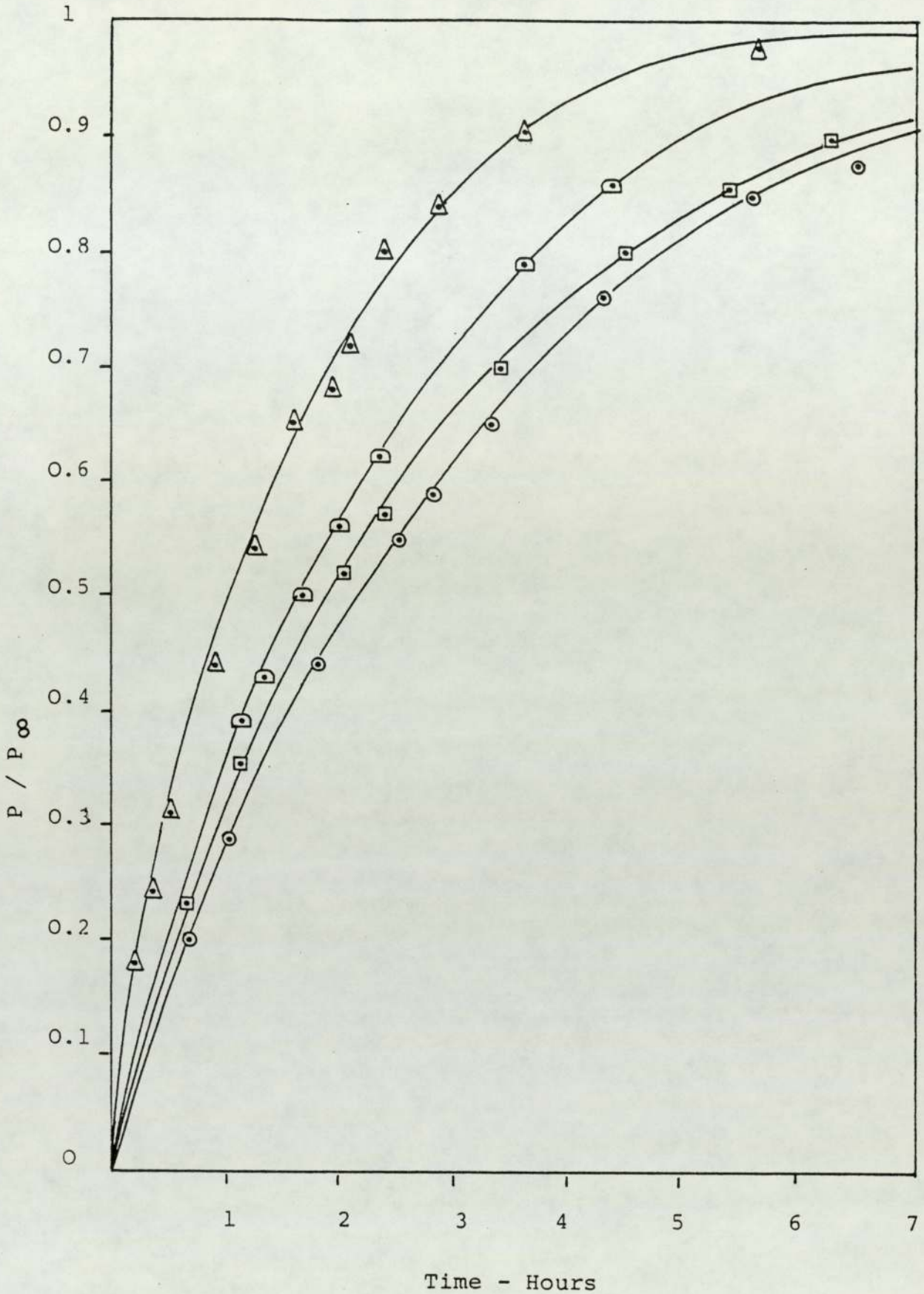


Figure 3.4 Initial rate curves for the decomposition of DMAC in nitrobenzene at 59°C $[DMAC]_o$ = 0.50 mol litre^{-1}

⊙ [Pyridine] = 0.125 mol. litre^{-1}

⊡ [Pyridine] = 0.25 mol. litre^{-1}

⊙ [Pyridine] = 1.0 mol. litre^{-1}

△ [Pyridine] = 1.5 mol. litre^{-1}

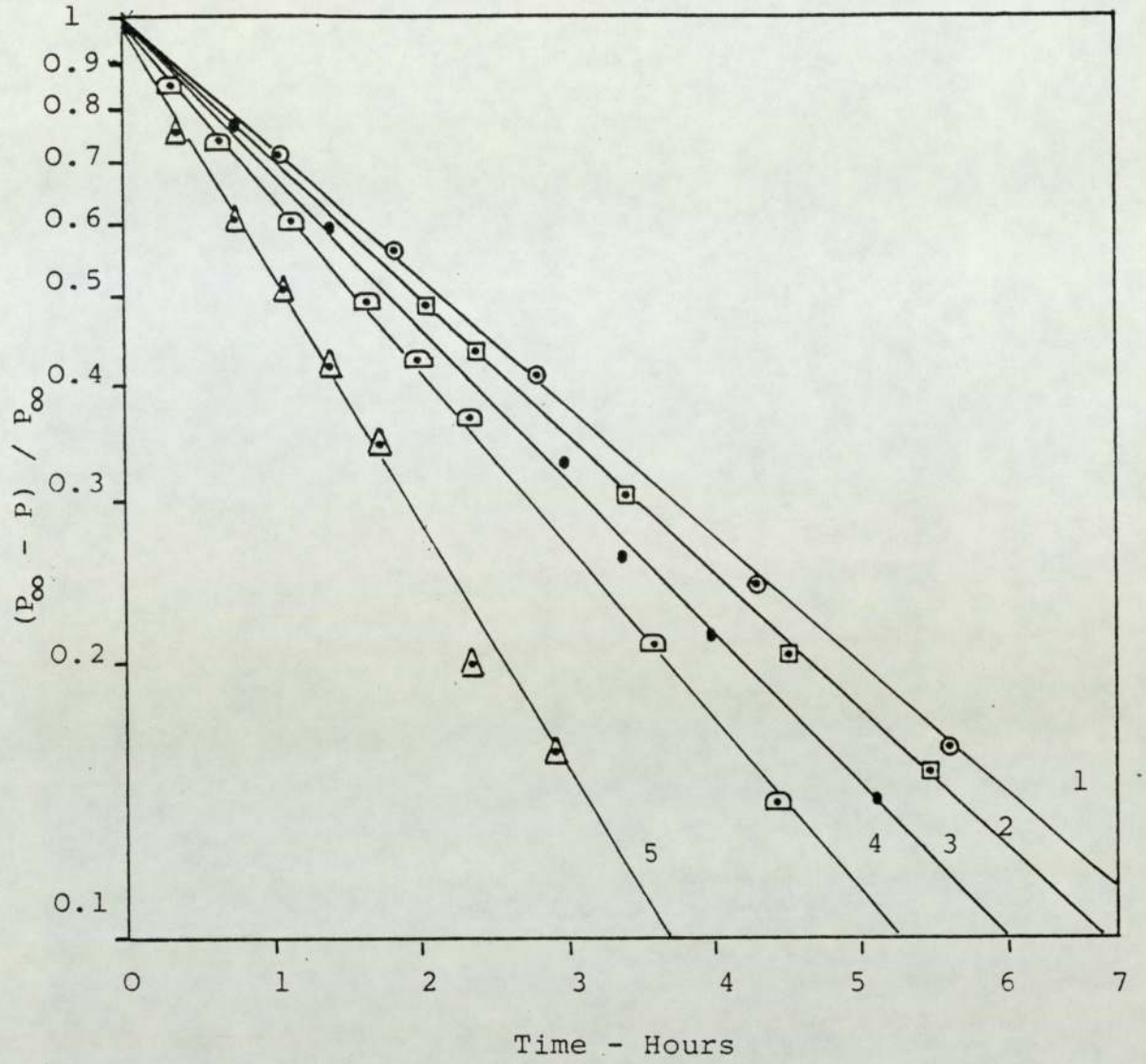


Figure 3.5 First order (semi-logarithmic) plots for the decomposition of DMAC in nitrobenzene at 59°c $[DMAC]_o$ = 0.50 mol. litre^{-1}

(1) [Pyridine]= 0.125 mol. litre^{-1}
(2) [Pyridine]= 0.25 mol. litre^{-1}
(3) [Pyridine]= 0.50 mol. litre^{-1}
(4) [Pyridine]= 1.0 mol. litre^{-1}
(5) [Pyridine]= 1.5 mol. litre^{-1}

TABLE 3.2

First-order rate constants obtained for the decomposition of DMAC with various concentrations of pyridine at $59^{o}c$.

$$[DMAC]_{o} = 0.50 \text{ mol. litre}^{-1}$$

Pyridine Conc. Mol. $litre^{-1}$	$10^{5} k_{1}$ (Sec^{-1})
0.125	8.96
0.25	9.63
0.50	10.55
1.00	12.03
1.50	17.50

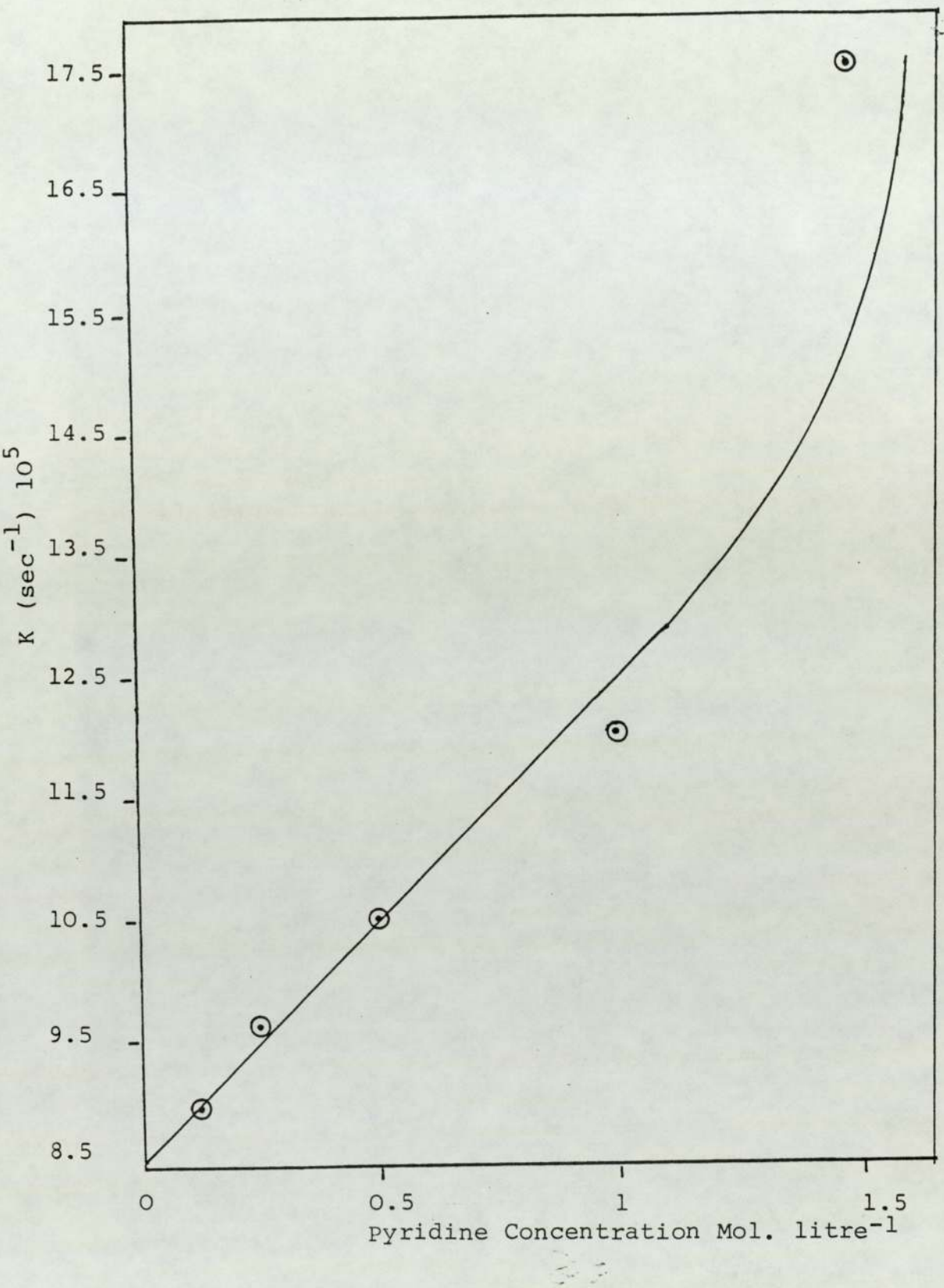


Figure 3.6 Plot of first - order rate constant versus [PY] for the decomposition of DMAC with pyridine at 59°C

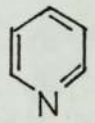
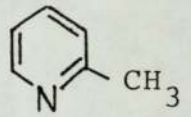
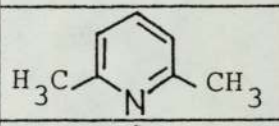
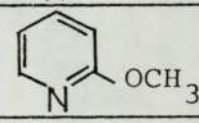
$[DMAC]_o$ = 0.50 mol. litre^{-1}

incorporation of methyl groups as substituents on the pyridine ring. Thus the series; pyridine, 2 - methyl pyridine (α- picoline) and 2, 6 - dimethyl pyridine (2,6 - Lutidine) (Table 3.3) represents an increase in nucleophilicity of the nitrogen with increase in ring substitution. Figure (3.7) shows the initial rates for the decomposition of DMAC with a series of substituted pyridines and Figure 3.8 shows the semi - logarithmic plot from which the second order rate constants are calculated and presented in table (3.3). In all cases equimolar amounts of the pyridine and DMAC were used. The results would suggest that for a sterically hindered anhydrocarboxylate monomer, eg. DMAC, the steric effect of the substituted pyridine is more important than the nucleophilicity of the tertiary base in determining the rate of reaction. A drastic reduction occurs in the rate constant when the tertiary base, 2 - methoxy pyridine is used. In this case the steric hindrance of the substituent group is coupled with a decrease in nucleophilicity of the nitrogen by the inductively electron withdrawing methoxy substituent. This will be discussed in more detail in Chapter 4.

Table 3.3

Second-order rate constant for the decomposition of DMAC with a series of substituted pyridines at 59°c

$[DMAC]_o$ = 0.50 mol. litre^{-1}

Substituted Pyridine		pKa	$10^5 k_2$(l. mol.$^{-1}$ sec.$^{-1}$)
Pyridine		5.17 (a)	21.10
2 - methyl pyridine (∝ - picoline)		5.97 (a)	9.62
2,6 - Dimethyl pyridine (2,6 -Lutidine)		6.75 (a)	8.75
2 - Methoxy pyridine		3.3 (b)	1.18

(a) obtained from reference (103)
(b) obtained from reference (104)

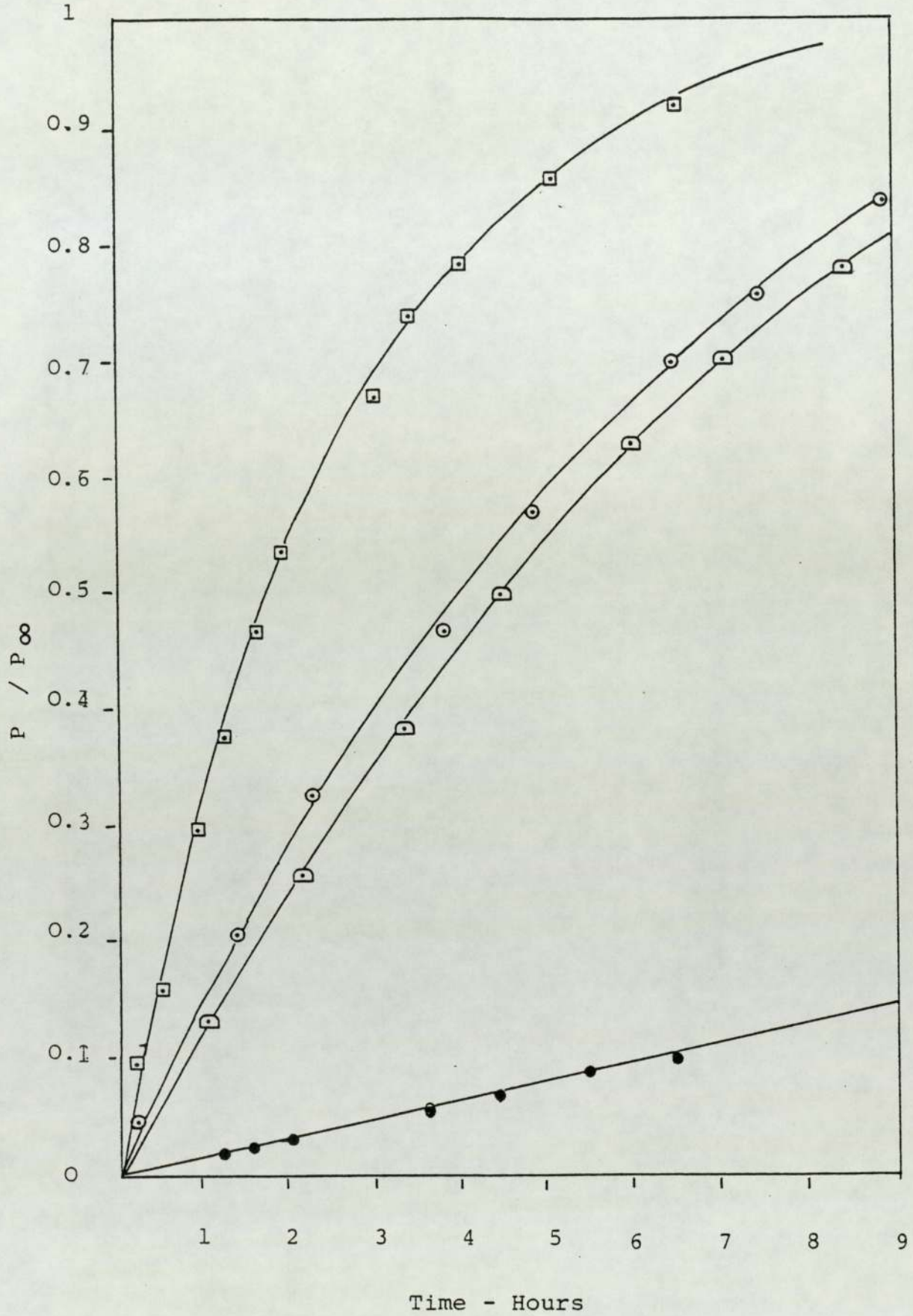


Figure 3.7 Rate curves for the decomposition of DMAC in nitrobenzene at 59°C.

$[DMAC]_o$ = 0.50 mol. litre^{-1}

⊡ [pyridine] = 0.50 mol. litre^{-1}

⊙ [α-picoline] = 0.50 mol. litre^{-1}

◘ [2,6-Lutidine] = 0.50 mol. litre^{-1}

● [2 - methoxy pyridine] = 0.50 mol. litre^{-1}

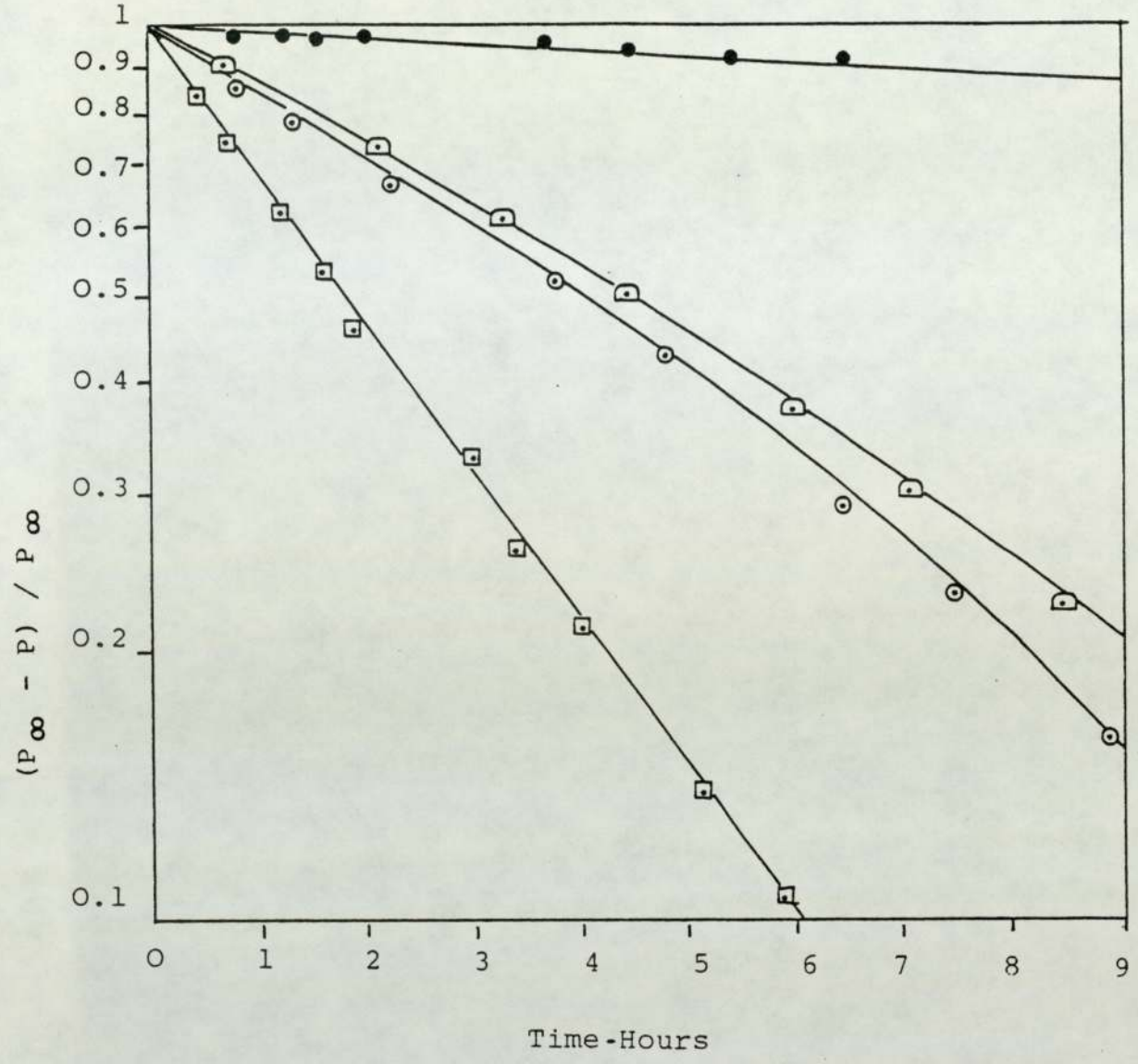
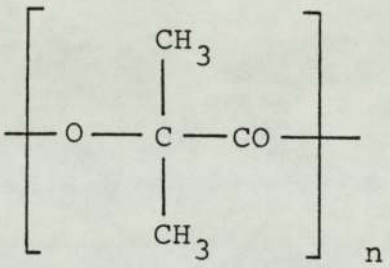


Figure 3.8 First-order (semi-logarithmic) plots for the decomposition of DMAC in nitrobenzene at 59°C $[DMAC]_o$ = 0.50 mol. litre^{-1}

- ⊡ [Pyridine] = 0.50 mol. litre^{-1}
- ⊙ [∝ - picoline] = 0.50 mol. litre^{-1}
- ⊙ [2,6-Lutidine] = 0.50 mol. litre^{-1}
- ● [2 - Methoxy pyridine] = 0.50 mol. litre^{-1}

3.1.5 Nature and Characterisation of Reaction Products

A study of the decomposition products of the reaction of DMAC with pyridine and substituted pyridines demonstrated that in each case carbon dioxide, polymer and tertiary base were the only products. The tertiary base was not associated with the polymer and the structure of the polymer was consistent with that of a poly - ∝ - ester (XII), where the value of (n) is governed by the purity of the system.



(XII)

Polymers samples from DMAC with a range of pyridine and substituted pyridine with different concentration were prepared under reduced pressure by using carius tubes which described in chapter 2. The white precipitate formed after the reaction completed was separated from the solution by centrifuging and the solvent was removed under vacuum at 40°C. The precipitate treated with ether to remove traces of impurities, was-finally dried under vacuum at room temperature for several hours. After drying, the melting point of the polymer was determined by Gallenkemp melting point apparatus. The melting point of the polymers range from 172 - 176 °C which is characteristic of low molecular weight DMAC polymer. The polymer sample is soluble in THF at 40°C (it is believed that the low molecular weight polymers are soluble in THF).

The polymer samples were examined by gel permeation chromatography and additionally characterised by infra - red, n.m.r. and mass spectra techniques. Infra - red spectra were record as KBr discs and the spectra obtained is shown in Figure (3.9). The strong absorption shown at 1740 cm^{-1} is well known to be characteristic of backbone ester carbonyl of poly - α - ester, together with methyl absorption at 1385 cm^{-1}. The n.m.r. spectrum of poly DMAC was obtained with a 10% W/V solution in deuterated chloroform and the produced spectra were entirely consistent with the presence of methyl group protons in a structural environment corresponding to poly DMAC (XII). Figure (3.10) shows a typical change in proton nuclear magnetic resonance from α - hydroxy isobutyric acid (A) to monomer DMAC (B) and finally to the poly DMAC (C). The polymer showed a high degree of crystallinity in terms of sharp lines in their X - ray powder diffraction photograph (Figure 3.11)

Molecular Weight Study :-

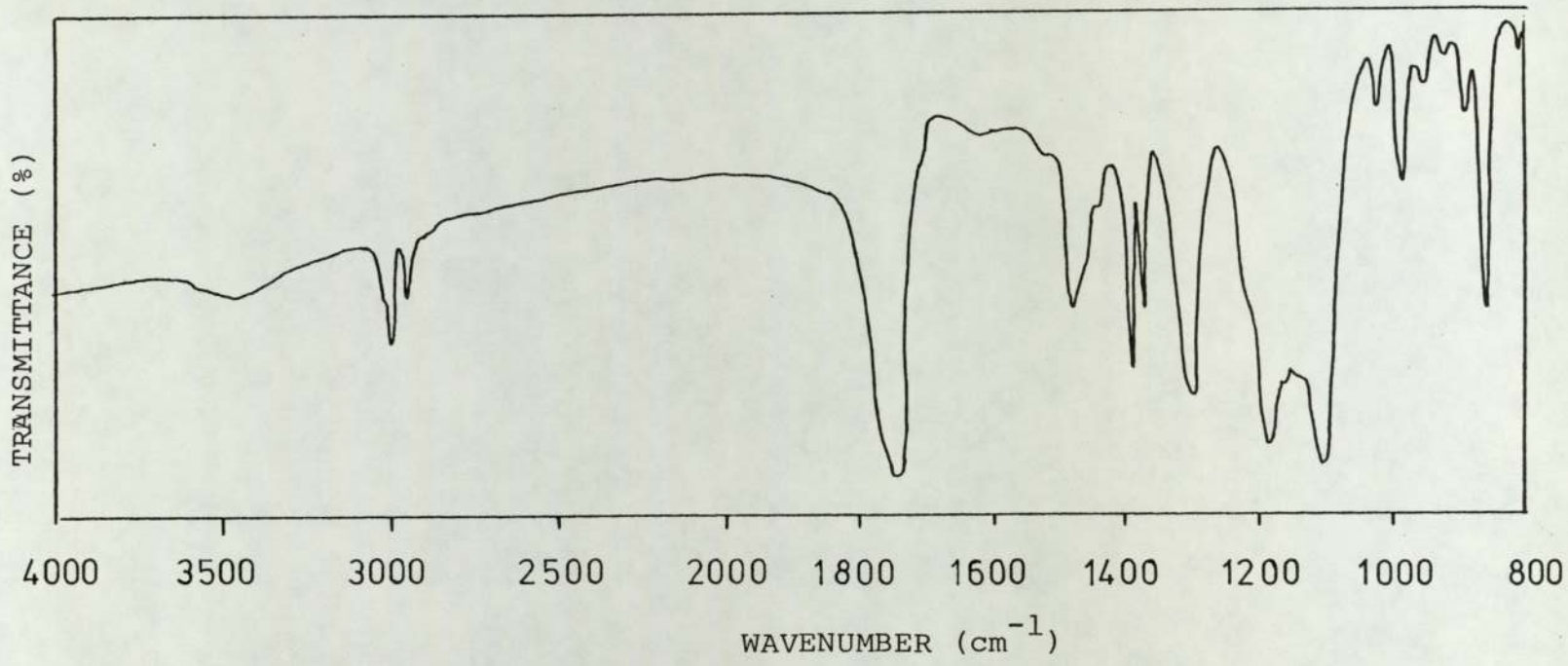
Determination of molecular weight and molecular weight distribution were carried out by RAPRA by using gel permeation chromatography techniques. The principal of G.P.C. was discussed in chapter 2 and the following variables were used:-

Flow Rate	1 ml per minute
Solvent	Tetrahydrofuran
Temperature	Ambient

The results are presented in Table (3.4), are from a series of experiments involving the study of various effects on the molecular weights of poly - α - esters obtained from the

Figure 3.9

Infra-red spectrum of poly DMAC obtained by the decomposition of DMAC in Toluene as solvent using pyridine. KBr disc reference air.



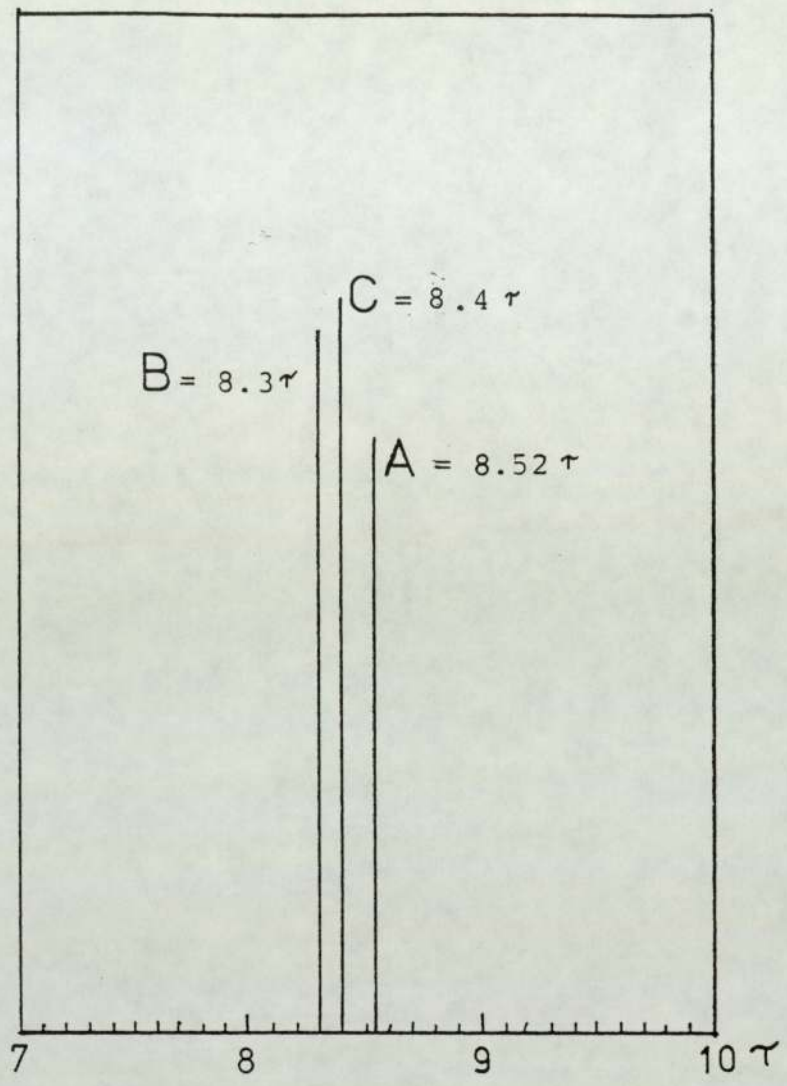


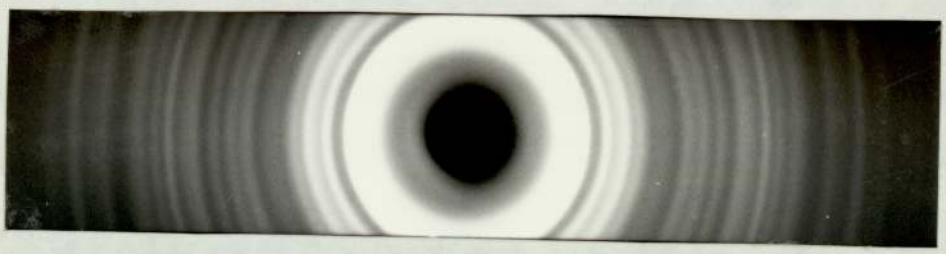
Figure 3.10 NMR spectra of :

(A) ∝ - hydroxy isobutyric acid

(B) DMAC

(C) poly DMAC

Figure 3.11



POLY - DMAC

TABLE 3.4

Gel Permeation Chromatography of

Poly -α- ester derived from Pyridine

initiated polymerisation of DMAC

(A) Effect of Temperature

$[M]_o = [PY]_o$ Solvent : Nitrobenzene

Temperature ^oC	$\bar{M}_n$	$\bar{M}_w$	$\bar{M}w$ / $\bar{M}n$	Highest MW
40	1931	2095	1.08	5310
50	2019	2129	1.05	4024
60	2036	2177	1.07	6040

(B) Effect of $[M]_o$ / $[PY]_o$ Temperature = 50^oC
Solvent = Nitrobenzene

$[M]_o$ molar	$[PY]$ molar	$\bar{M}n$	$\bar{M}w$	$\bar{M}w$ / $\bar{M}n$	Highest MW
1	0.5	1856	1999	1.08	5479
1	1	2019	2129	1.05	4024
1	1.5	1791	1859	1.04	4251

(C) Solvent Effect

$[M]_o = [PY]_o$ Temperature = 60^oC

Solvent	$\bar{M}n$	$\bar{M}w$	$\bar{M}w/\bar{M}n$	Highest MW
Nitrobenzene	2036	2177	1.07	6040
Toluene	2010	2119	1.05	5831

decomposition of DMAC with pyridine. It is relevant to note that the molecular weight distribution of most samples studied in this work lie in the range 1.05 — 1.08 as shown in Table (3.4). The related discussion is contained in chapter 4.

3.2 The Reaction of DMAC with Pyridines: Preliminary Conclusions

In this section some preliminary conclusions are drawn from the results in this chapter. A more detailed discusssion of the polymerisation of anhydrocarboxylates with tertiary bases is contained in the next chapter (4).

The decomposition of DMAC in the presence of pyridine and substituted pyridines resulted in the formation of a poly - α - ester (XII) with the evolution of gaseous carbon dioxide. This has many potential advantages over purely thermal polymerisation of this anhydrocarboxylate. In comparison to the reaction of DMAC with equimolar quantity of pyridine, which has a half - life ($t_{1/2}$) of 2 hours at 58° C the half - life for the thermal decomposition of DMAC is 1050 hours at 90° C in the same solvent (nitrobenzene). Similarly polymerisation of DMAC by nucleophilic (protonic) initiation is sterically hindered by the two ring methyl groups present at C(5) and does not proceed at a measurable rate. Thus pyridine initiation provides an extremely valuable method for ring - opening of this anhydrocarboxylate.

The kinetic parameters obtained from the pyridine initiated polymerisation (Table 3.1) are similar to those

previously obtained from the polymerisation of other anhydrocarboxylates with pyridine under similar conditions. The similarities between these monomers will be disussed in more detail in chapter 4. The value of activation energy for DMAC decomposition with pyridine is 82 K.J. $mol.^{-1}$ which is less than the activation energy required for thermal decomposition ($\sim$ 100 - 120 K.J. $mol.^{-1}$) and higher than that for primary and secondary amine initiated polymerisation of unsubstituted or monosubstituted NCA s (I) or anhydrocarboxylates of α-hydroxy acids (Ea = 25 - 48 K.J. $mol.^{-1}$).

The most important features which must be accommodated in any mechanism which will explain the results in this chapter, are listed below:

(i) The reaction is kinetically first - order with respect to both monomer and pyridine.

(ii) The fact that the effective pyridine concentration is not consumed during the course of the reaction.

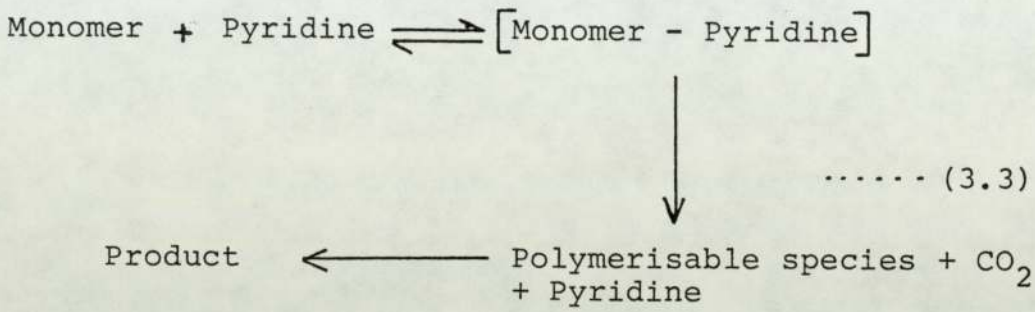
(iii) Pyridine is not associated with the polymer.

(iv) The molecular weight of the polymer produced is not governed by the initial concentration of pyridine and the molecular weight distribution is narrow ($\bar{M}w/\bar{M}n \approx 1.07$).

(v) The molecular weight is controlled by the presence of moisture or other nucleophiles (eg. parent acid).

(vi) The structure of the resultant poly - α- ester contains hydroxyl and carboxyl groups as end groups.

There are various interpretations of a reaction mechanism. Below is shown a scheme (Equation 3.3) which is capable of most accurately representing the balance of observed effects and which was first suggested by Smith[90] in connection with the polymerisation of other anhydrocarboxylates.

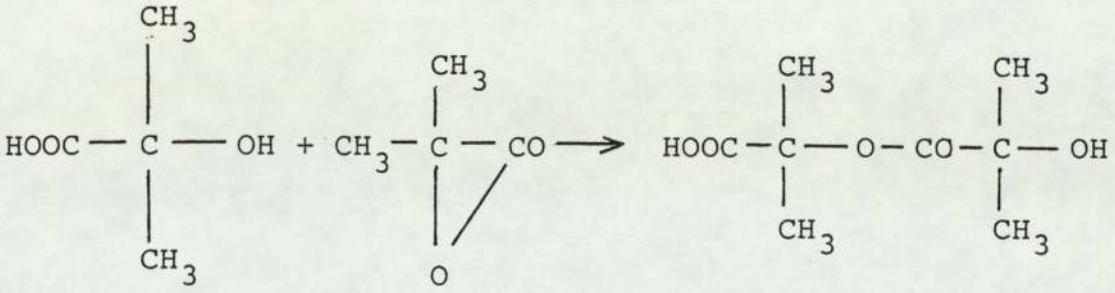


..... (3.3)

The mechanism involves the formation of an intermediate between the monomer and tertiary base which rapidly decarboxylates to yield a polymerisable species capable of taking part in a chain propagation process.

The structural characteristics of the polymer produced from DMAC with pyridine are identical to those encountered in thermal polymerisation of this monomer. This suggests comparable chain growth processes in the two cases and the possibility of the involvement of an α - lactone as the polymerisable intermediate , indicated in Equation (3.3). This is supported from the results which are presented in this chapter . Thus the effect of moisture and parent acid on the molecular weight, and the presence of a hydroxyl and a carboxylic acid group are both consistent with established chain growth reactions of α - lactone in the presence of

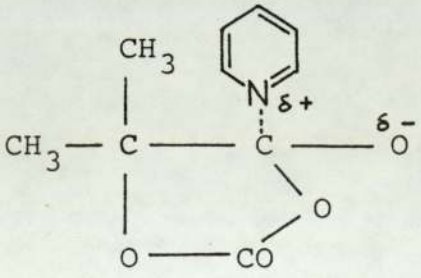
species of this type (Equation 3.4)



..... (3.4)

The involvement of the α- lactone would also account for the fact that the molecular weight is independant of the initial pyridine concentration since the pyridine molecule is involved only in the formation of the α - lactone and not in its subsequent behaviour.

Ring - opening reaction of anhydrocarboxylates, for example, mandelic acid anhydrocarboxylates (IX; R^1=H, R^2=C_6H_5) with nucleophiles[70] has shown that the C-4 carbonyl is the exclusive site of attack of this type of interaction. It is reasonable therefore, to assume that any interaction between the nitrogen lone pair in the pyridine molecule and the ring (DMAC) will occur at an electrophilic site such that centered at C - 4. The nature of the intermediate suggested in equation (3.3) may involve a form of a charge - transfer complex represented in (XIII). Such species would not be expected to occur as a stable isolated compound, and because the concentration of the charge - transfer complex prior to decomposition (Equation 3.3) is small compared to the overall



(XIII)

concentration of pyridine, the detection of such complexes using infra - red spectroscopy is difficult. The strength of the charge - transfer bond will depend mainly upon the nucleophilicity of the nitrogen , the susceptibility of the C - 4 carbonyl to this form of attack, and the steric hindrance associated with both the heterocyclic base and methyl groups at C - 5 of DMAC. Thus the higher activation energy value for decomposition of DMAC with pyridine (compared to ring opening with protonic nucelophiles) is due to a higher energy of the highly sterically hindered activated complex (XIII).

A study of variably substituted pyridines (Table 3.3) particularly tertiary bases that are more sterically hindered than pyridine has been examined. The increase in rate due to decrease in nucleophilicity of the nitrogen is very nearly balanced by an increase in reactivity due to the steric repulsion of the additional substituents (methyl groups). The decomposition of DMAC in the presence of substituted pyridine leads in all cases, to the formation of polymer. Pyridine had more effect in the decomposition of DMAC than α - picoline (2 - methyl pyridine) and 2, 6 - Lutidine (2,6 dimethyl pyridine) (Figure 3.7). The use of a weak base, 2 - methoxy pyridine resulted in a considerable reduction in the rate of reaction, indicating the importance of the basicityof the attacking base. The results (Figure 3.8) show similar kinetic behaviour in that first - order dependence on initial initiator concentration is observed throughout the reaction.

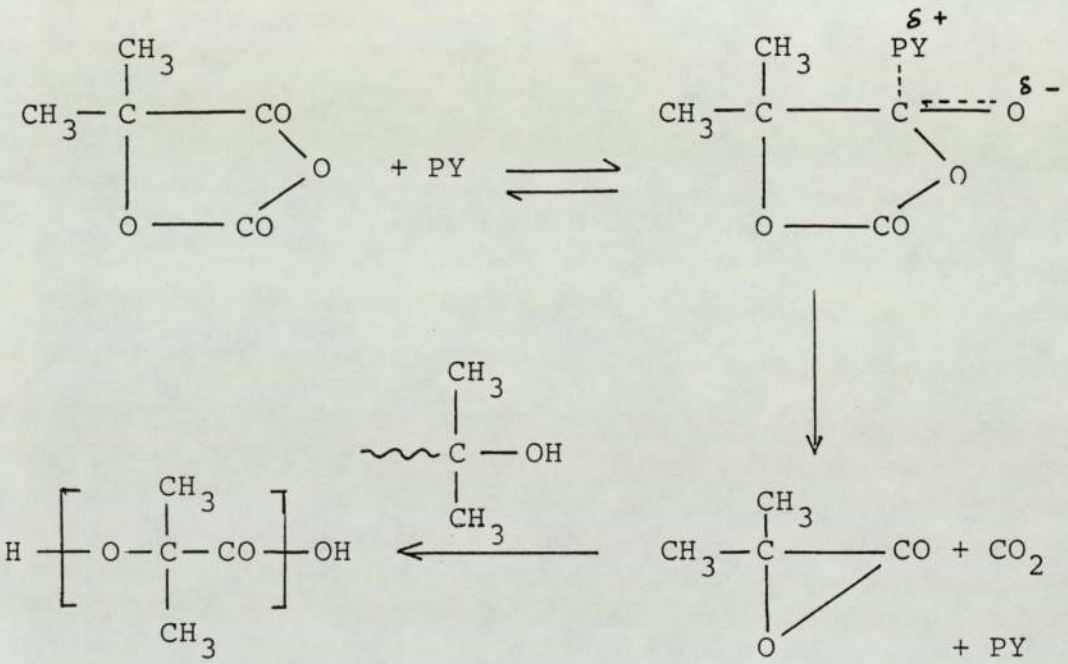
The effect of varying the pyridine concentration has been discussed. Within experimental error it was found that

the rate of decomposition of DMAC increased with increasing pyridine concentration (Figure 3.5). The reaction shows first - order dependence on residual monomer (Figure 3.6). At higher pyridine concentration ($[PY] = 1.5$ mol. litre^{-1}), deviation from first order dependence on pyridine concentration occurs. This appeared clearly, where the linear plot (Figure 3.6) begins to show a slight curvature. This deviation can be probably explained by the fact that as the concentration of pyridine increased, the solvent medium characteristic varied leading to increase in solvent donicity.

In addition to the kinetic parameters, information relating to factors affecting the molecular weight and structure of the polymer are important in considering the possible polymerisation mechanism. Poly - α - esters of DMAC, Poly (α - hydroxy isobutyric acid), obtained from pyridine initiated polymerisation are found to have relatively low molecular weight, in spite of purity of the solvent (nitrobenzene), monomer, and pyridine. This may be due to presence of moisture or hydrogen - containing impurities (eg. primary and secondary amines) in the pyridine which causes the lowering of molecular weight of the resultant polymer. Variation in initial concentration of pyridine, in temperature and change in solvent medium failed to produce any noticeable effect on molecular weight. X - ray photographs of the polymer from DMAC with pyridine (XII) which are shown in Figure (3.11)indicated that the polymer was crystalline. The crystallanity of poly DMAC is due to high interchain cohesion consequent upon the highly polar nature of the backbone (high ratio of polar to non polar units in the backbone)

and the symmetrical nature of the substitution pattern.

In the light of the results which are presented in this chapter, the sequence of reactions leading to the formation of polymer may now be formulated. The proposed mechanism involves the fragmentation of the 1,3 - dioxolan - 2,4 - dione ring as a charge - transfer complex and loss of carbon dioxide, with the formation of an α- lactone. The reaction sequence is shown in Equation (3.5), in which the α - lactone takes part in a rapid chain propagation step with the terminal hydroxyl group of a polymer chain.



..... (3.5)

The loss of pyridine from the intermediate structure enables the initiating molecule to take part in further reactions. The role of pyridine may, therefore, be considered to enhance the decomposition of the DMAC to form a polymer-

isable species, the α- lactone, which takes part in a chain growth reaction.

Reconsideration of the Equation(3.5)shows that the rate of the pyridine initiated polymerisation of DMAC is governed by two factors, the equilibrium constant of the complex formation and the rate of decomposition of the complex to α - lactone. Thus the equation implies that the activation energy of the overall reaction does not refer to a single process.

The decomposition of DMAC in the presence of pyridine, whilst yielding the corresponding poly - α - ester, proceeds at a rate slower than would be needed for efficient copolymerisation with unsubstituted monomers. Use of stronger bases such as lithium tertiary butoxide or sodium methoxide (Chapter 5) may present a degree of reactivity which could be exploited for the low temperature polymerisation of this monomer.

CHAPTER 4

THE TERTIARY BASE INITIATED POLYMERISATION OF ∝ - HYDROXY ACID ANHYDROCARBOXYLATES :-

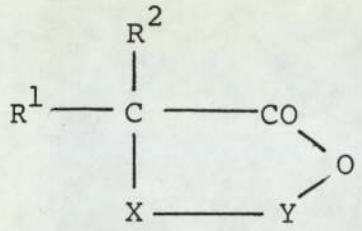
DISCUSSION

The decomposition of substituted anhydrocarboxylates (IX), in the absence of the added initiators is not a satisfactory method of polymer formation, for a number of reasons. Firstly, the thermal stability is such that lengthy reaction times are required and in order to reduce this time, higher temperatures must be used. Such reaction conditions increase the susceptibility of the monomer to a secondary fragmentation process, yielding carbon monoxide and a ketone, or aldehyde, which considerably reduces the yield of polymer . It is evident, therefore, that a more suitable mode of polymerisation would be by the use of an initiator, for example protonic or aprotic nucleophiles. For this type of polymerisation, a necessary requirement is that the monomer must contain an active site and be susceptible to attack by a regenerated species.

In this chapter, the following points will be discussed:

(i) The nature of the reaction of DMAC with pyridine in the light of the results in Chapter 3 and in comparison with results from previous studies including thermal and protonic decomposition of DMAC.

(ii) Comparison of DMAC with the following cyclic monomers



R^1	R^2	Y	X	
CH_3	CH_3	CO	O	DMAC
CH_3	CH_3	SO	O	HBAS
CH_3	CH_3	CO	S	TIBAC

(iii) The mechanism of the reaction between pyridine and the anhydrocarboxylates and comparison with the mechanisms of polymerisation of ∝ - amino - N - carboxy anhydride by tertiary amine.

The ring opening reactions of dimethyl substituted anhydrocarboxylates, in particular thermal decomposition, have been studied by Tighe [19]. The first - order rate constant was found to be 1.0×10^{-7} sec.$^{-1}$ in nitrobenzene at 90°c. At this point it is interesting to compare the reactivity of DMAC towards protonic - initiated polymerisation and thermal polymerisation. A value of $k_b = 0.8 \times 10^{-8}$ l. mol^{-1}. sec^{-1}. was obtained for the reaction of DMAC with benzyl alcohol under the same conditions as that in thermal polymerisation. It was suggested that the reason for such low reactivity was the nucleophilicity of the hydroxyl group being insufficient to overcome the steric hindrance of the ring C(5) substituents. The bimolecular reaction with the C(4) carbonyl does not occur and the product, benzyl ∝ - hydroxy isobutyrate, is formed as a result of reaction of the ∝ - lactone, (the thermal ring extrusion product), with an hydroxyl group. Methyl substituents,

being inductively electron donating,cause some deactivation of the C (4) carbonyl. From Table (4.1), which shows the rate constants for the decomposition of DMAC from thermal, protonic and aprotic initiated polymerisation, it can be seen that pyridine initiation provides an extremely rapid method of ring - opening for compounds of the type discussed here. In addition, since the pyridine concentration does not govern the molecular weight of the product the effective rates of polymerisation by this method of initiation can be very high.

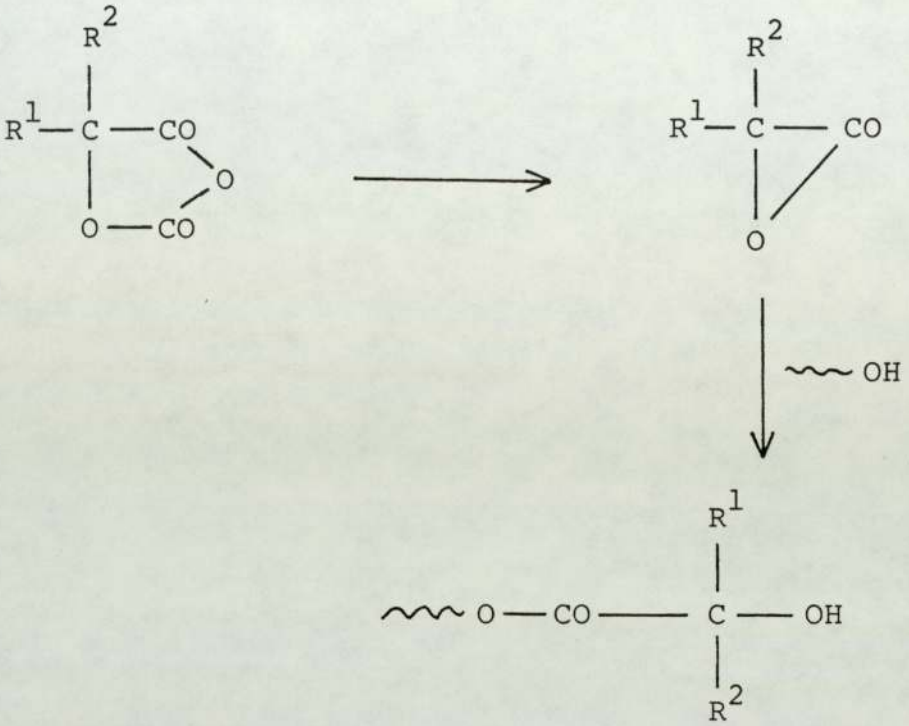
Table (4.1)

Rate constants for decomposition of DMAC with different polymerisation methods in nitrobezene

Polymerisation	Rate constant	Temperature ^{o}C
Thermal	1.0×10^{-7} $sec.^{-1}$	90
Protonic initiated (Benzyl alcohol)	0.8×10^{-8} $l.mol.^{-1}$ $sec.^{-1}$	90
Aprotic initiated (pyridine)	2.93×10^{-4} $l.mol.^{-1}$ $sec.^{-1}$	60

The substituents on the C5 carbon play an important role in the understanding of the suggested mechanism since this involves the attack of the nucleophile at the C-4 carbon of the anhydrocarboxylate.The reactivities of a series of

anbydrocarboxylate rings with pyridine at a fixed temperature and in the same solvent mediumare determined by the nature of the substituents on the rings, which subsequently reside on the growing chain of the polymer ie.



One aim of ring-opening studies of this type is to extend the understanding of steric and polar interactions in the monomer and in the propagating end group. The ultimate aim is the development of multiple correlation equations to enable rates of polymerisation to be predicted. Correlation of the relative magnitude of the steric effect and the electronic or polar effect of a substituent in an aliphatic molecule with the measured rate of a chemical reaction can be achieved with reasonable accuracy by using the Taft equation. The Taft $\rho^{*}\sigma^{*}$ Equation (4.1) relates a reaction rate k, with σ^{*}, a parameter representing the polar or electronic effect of a substituent, and ρ^{*}, an empirical parameter dependent upon the nature of the reaction and the reaction conditions.

$$\log \frac{k}{ko} = \rho^* \sigma^* \qquad \text{----------(4.1)}$$

Deviations from Equation (4.1) may be due to steric effects associated with the reaction, and equation (4.2) may be used

$$\log \frac{k}{k_o} = \rho^* \sigma^* + sE_s \text{ -----(4.2)}$$

Equation (4.2) may be rewritten, thus,

$$\log k = \rho^* \sigma^* + sE_s + C \text{ ---(4.3)}$$

Where C is a constant dependent upon the interactive process. Similarly E_s is considered as a steric substituent constant governed by an empirical parameter s. Thus the parameters ρ^* and s reflect the relative importance of the polar and steric effect. In the monomer of the general type (IX), with different substituents R^1, R^2, the reaction rates at 60^oC, in the presence of equimolar pyridine in nitrobenzene as a solvent, provide a basis for comparison. The rate constants together with combined polar and steric parameter values are shown in Table (4.2). The best fit is obtained where a value of 1.88 is given to ρ^* and 1.29 to s, this is illustrated in Figure (4.1). The importance of this is that it provides support for the concept of pyridine attacking the C - 4 carbonyl in the ring and being subject to the steric restriction imposed by the C - 5 ring substituents and their ability to activate the C - 4 carbonyl.

The proposed mechanism for the decomposition of anhydrocarboxylate in the presence of pyridine involves the

TABLE (4.2)

Substituents on the C - 5 carbon of an anhydrocarboxylate ring, second - order rate constants for pyridine initiated polymerisation at 60°C in nitrobenzene and the polar and steric parameters.

Monomer	R^1	R^2	k_2 at 60°c Mole^{-1} litre sec.$^{-1}$	σ^* (1)	E_s (1)	$1.88\sigma^* + 1.29\ E_s$	$2\sigma^* + 1\ E_s$
MAAC	C_6H_5	H	1200×10^{-4}	1.09	0.74	2.99	2.92
AAAC	C_6H_5	CH_3	1.62×10^{-4}	0.6	-0.5	0.48	0.7
PFAAC	C_6F_5	CH_3	14.3×10^{-4}	1.10	- 0.5	1.42	1.7
BAAC	C_6H_5	C_6H_5	5.9×10^{-4}	1.2	- 1.0	0.96	1.4
GAAC	H	H	2560×10^{-4}	0.98	2.48	5	4.44
DMAC	CH_3	CH_3	2.93×10^{-4}	0	0	0	0

(1) Value obtained from reference (106)

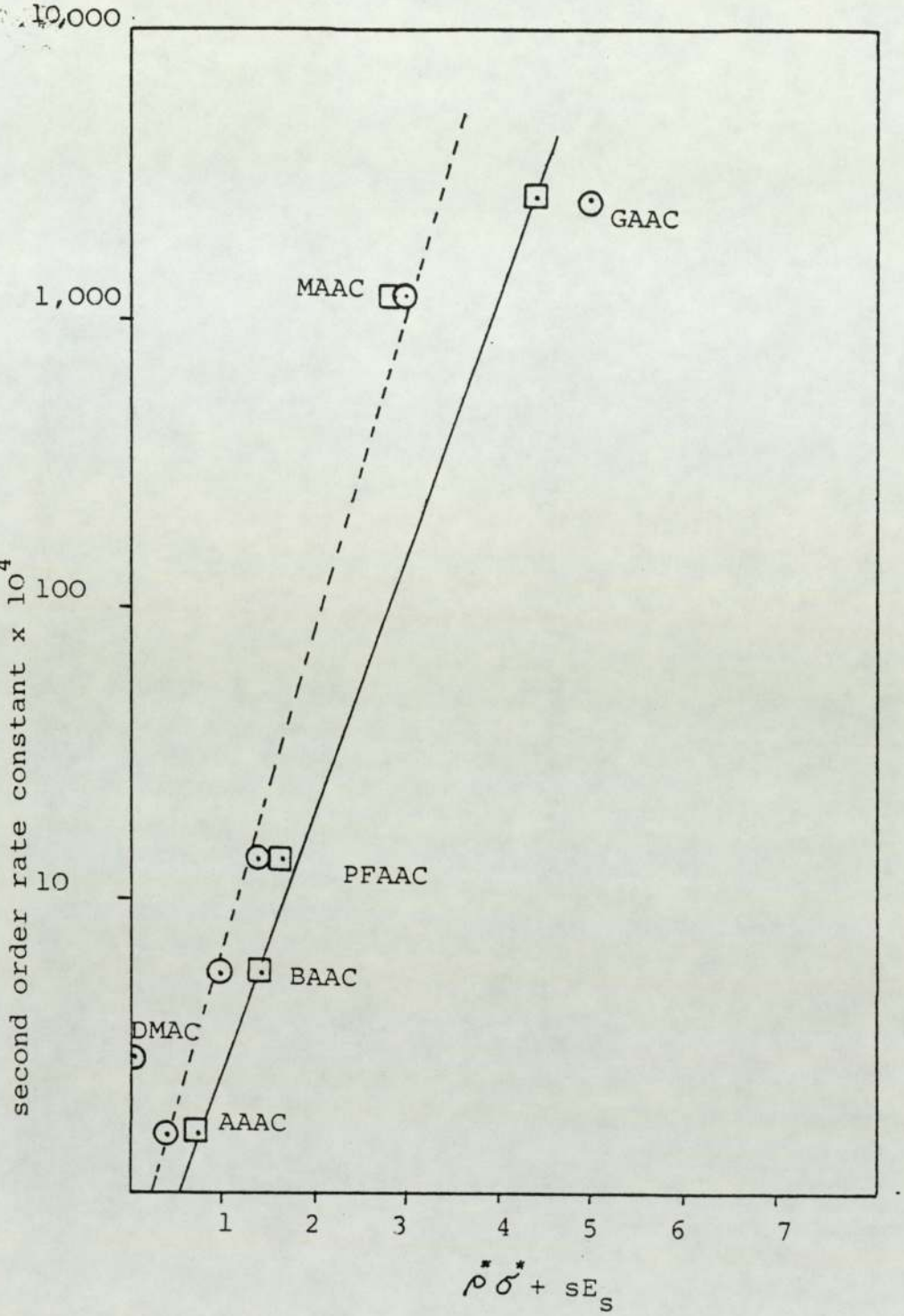


Figure 4.1 Semilogarithmic plot of second order rate constant against substituent parameters for the reaction between Pyridine and Anhydrocarboxylates.

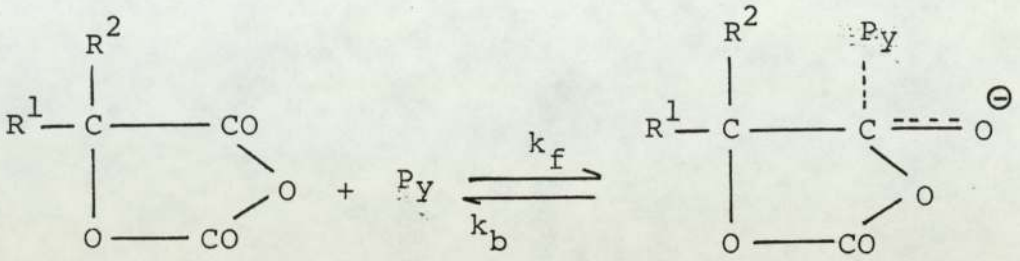
—— ⊡ $\rho^* = 2$, $s = 1$

----- ⊙ $\rho^* = 1.88$, $s = 1.29$

following stages: -

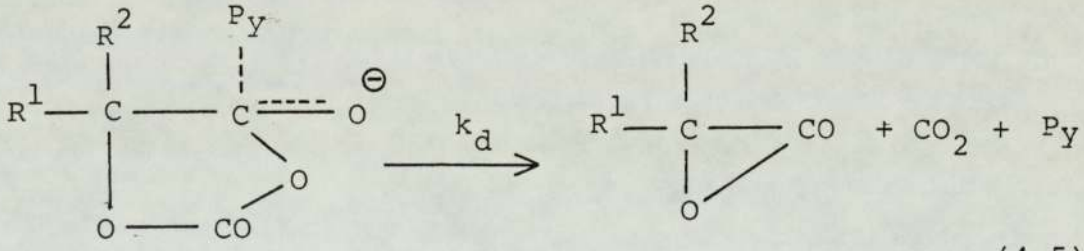
(i) The attack of pyridine on the C - 4 carbonyl of the ring producing a charge transfer complex.

Equation (4.4)



... (4.4)

(ii) Decomposition of the charge transfer intermediate to yield carbon dioxide with the formation of a polymerisable species, (α - lactone), and pyridine. The α - lactone takes part in a rapid chain propagation step and would immediately polymerise to form a poly - α - ester



..... (4.5)

Where k_f : rate constant for formation of complex intermediate.

k_b : rate constant for breakdown of complex intermediate to form a monomer and pyridine

k_d : rate constant of decomposition of complex to the α - lactone.

The equilibrium constant K is given by: - $K = \frac{k_f}{k_b}$ ... (4.6)

$$\frac{d[\text{Product}]}{dt} = -\frac{d[M]}{dt} = k_d\,[MPY^*] \qquad \ldots\ldots\ldots (4.7)$$

Where $[MPY^*]$ represents the charge transfer complex which is produced from monomer $[M]$ and pyridine $[PY]$. The product is considered to be an α - lactone which takes part in a non-rate determining propagating reaction. The concentration of the intermediate $[MPY^*]$ and reactants are related through the equilibrium constant K.

(Equation 4.8)

$$[MPY^*] = K\,[M]\,[PY] \qquad \ldots\ldots\ldots\ldots (4.8)$$

Equation (4.8) now becomes

$$\frac{d[\text{Product}]}{dt} = k_d\,K\,[M]\,[PY] \qquad \ldots\ldots (4.9)$$

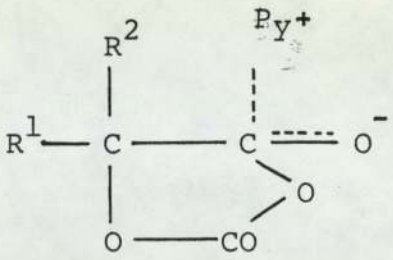
assuming that the concentration of $[MPY^*]$ is small compared to $[M]$, $[PY]$ and $[\text{Product}]$ (ie. that $[MPY^*]$ is a reactive intermediate). Comparison of Equation (4. 9) with Equation (3.1) gives

$$k_2 = k_d.\,K \qquad \ldots\ldots\ldots (4.10)$$

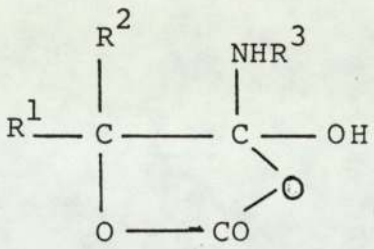
Equation (4.10) illustrates that the rate constant k_2 is governed by two factors, the equilibrium constant of the complex formation and the rate of decomposition of the charge transfer complex.

The nature of the species (XIV)produced in the pyridine - monomer reaction (Equation 4.5) will be quite different from transition state (XV) and products involved in the reaction of nucleophiles possessing transferable protons

(eg. primary amine)



(XIV)



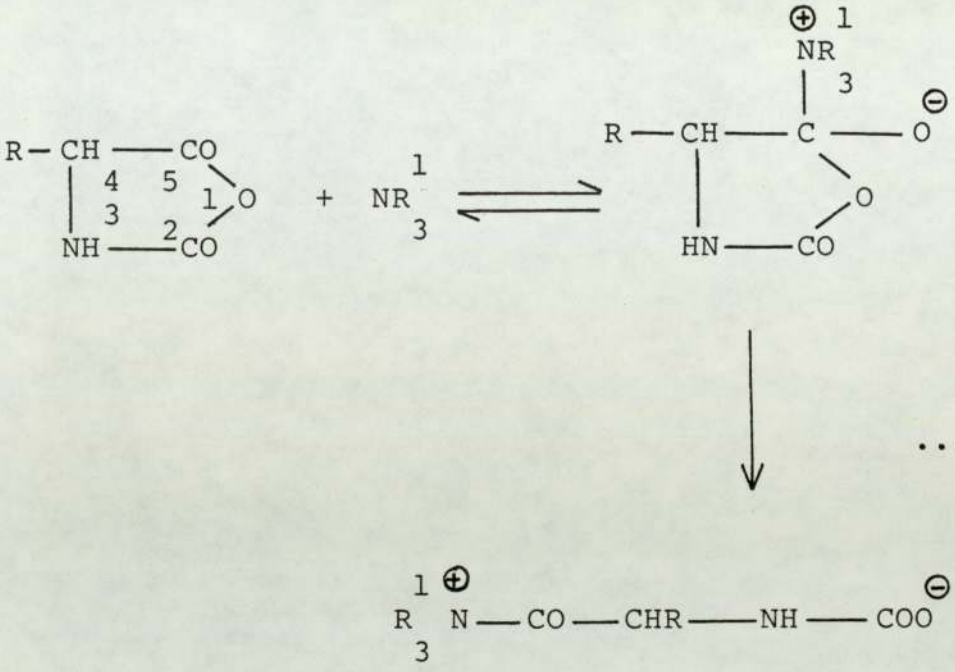
(XV)

The transferable proton allows valency considerations to be satisfied in the formation of a formal bond between the nucleophile and the C - 4 carbonyl of the monomer.

In the case of reaction with tertiary bases and anhydrocarboxylates, the ring is a strained system and the attacking base possesses no labile hydrogen and thus no rearrangement and proton shift can occur after bond scission and loss of carbon dioxide (Equation4.6). The role of pyridine may, therefore , be considered to greatly enhance the decomposition of the monomer to form a polymerisable intermediate , the α - lactone,which takes part in a chain growth reaction.

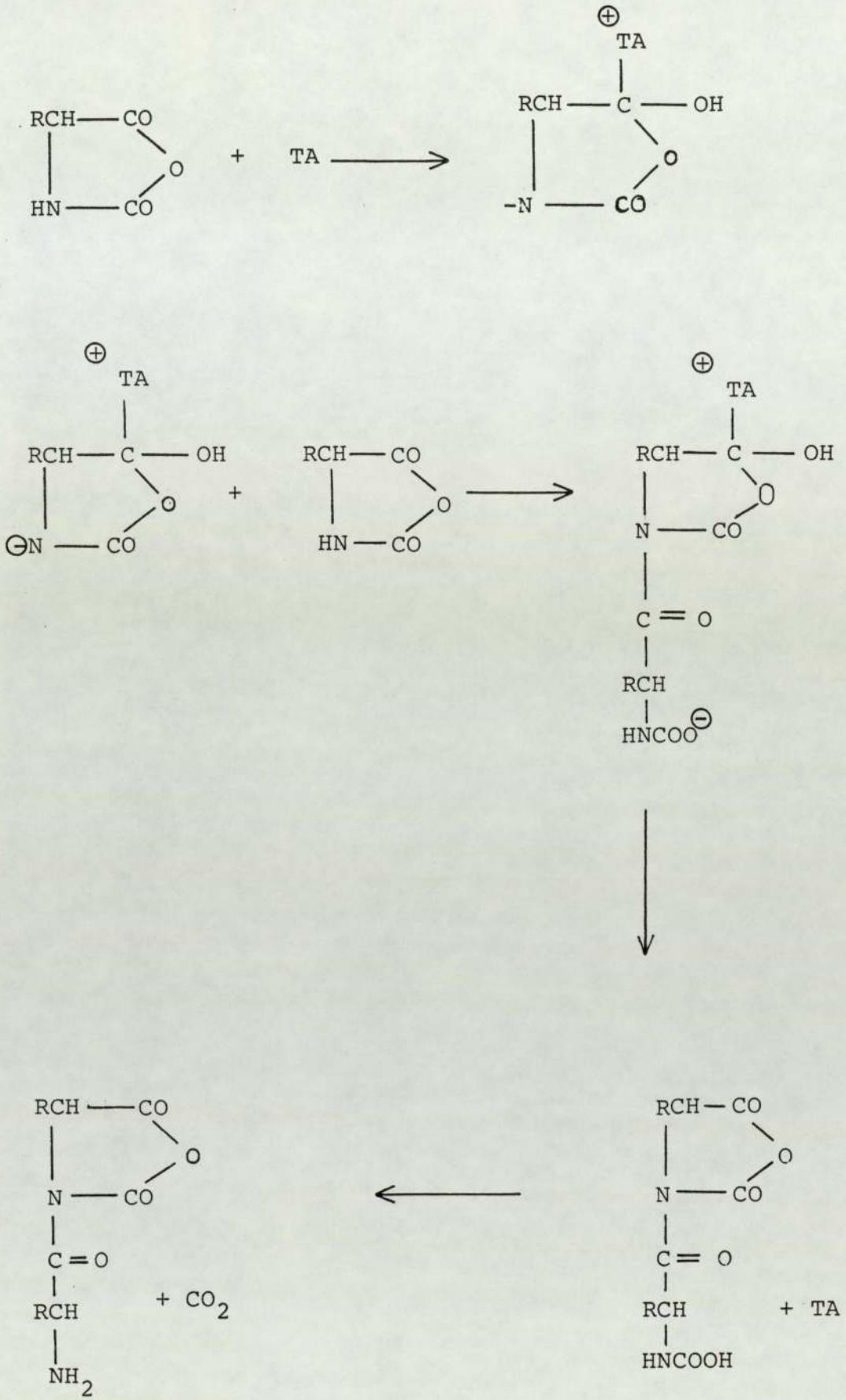
NCA derivatives of α - amino carboxylic acids can undergo polymerisation using tertiary amines. This polymerisation presents an interesting case to which the polymerisation of anhydrocarboxylates with pyridine may be compared. Several mechanisms were suggested to explain the tertiary amine initiation of NCA's , but no general mechanism was found. Weiland [107,108] suggested that the mechanism involves nucleophilic attack of an amine to the C (5) carbonyl to form

an intermediate tetrahedral complex which opens to form a Z witterionic molecule as shown in Equation (4.11). The reaction between the oppositely charged ends of the



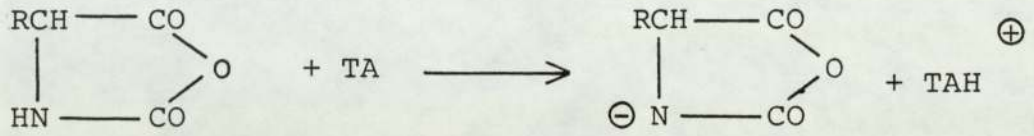
.... (4.11)

chains propogates the polymerisation and subsequent loss of the tertiary amine. This mechanism would explain the second order dependence on monomer but would require formation of the cyclic dimers and in practice no diketopiperazines were obtained. Ballard and Bamford [109] suggested a more likely alternative mechanism in which the role of the tertiary amine is to abstract the proton from the ring nitrogen via attack on the C - 5 carbonyl proton transfer, resulting in an anionic activated NCA which then attacks the C -5 carbonyl of a nonactivated molecule (Equation 4.12).



..... (4.12)

More recently, Bamford and Block [81] simplified the mechanism by assuming that the tertiary amine just acts as a base, abstracting a proton from the ring nitrogen rather than as a nucleophile attacking the C - 5 carbonyl.



..... (4.13)

The above mentioned mechanisms for tertiary amine initiated decomposition of NCA's, are not satisfactory to explain the proposed mechanism for the decomposition of anhydrocarboxylate with pyridine for a number of reasons. A Wieland - type mechansim would produce the analogous cyclic by - products, (the six member glycollide ring), of which none were detected as reaction products. The Bamford and Block mechanism is not feasible since it would require proton abstraction from the monomer molecule as the primary step and its kinetic requirements are second order dependence on monomer , and also that the base necessarily plays a part in the chain growth reaction.

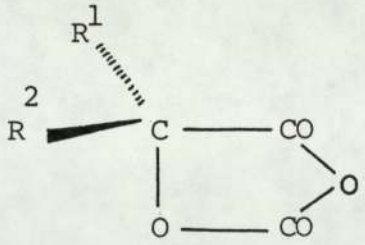
The kinetic parameters obtained from the pyridine initiated polymerisation of DMAC (Table 3.1) are very similar to those previously obtained from the polymerisation of other α - hydroxy acid anhydrocarboxylates under similar conditions. The results which are shown in Table (4.3) demonstrate that the reactivity of pyridine with anhydrocarboxylate depends on R^1 and R^2 (IX). Considering the situation and configuration of substituents at C - 5 (IX), it is to be expected that R^1 and R^2 will play a major

Table 4.3

Extrathermodynamic data for the pyridine initiated decomposition of anhydrocarboxylates at 60°C

Monomer	E_a K. J. mol^{-1}	A l. mol.$^{-1}$ Sec.$^{-1}$	$\Delta S^{\ddagger}$ J.K.$^{-1}$ mol.$^{-1}$
AAAC (89)	73.3	6.5×10^{7}	- 103
PFAAC (90)	62.5	6.9×10^{6}	- 157.3
MAAC (92)	48.3	4.3×10^{6}	- 163
GAAC (91)	49.07	1.31×10^{7}	- 117
DMAC	82.6	5.8×10^{8}	- 76.7
BAAC (90)	87.7	3.8×10^{11}	- 67.3

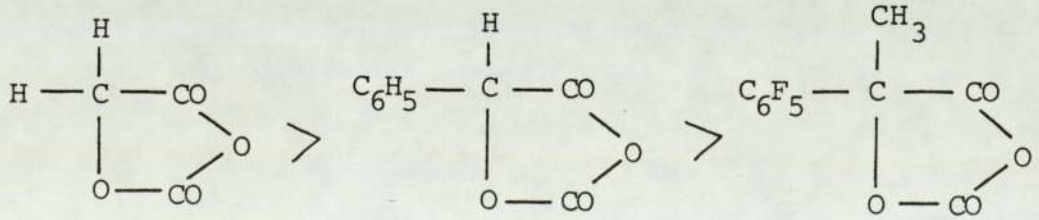
part in both



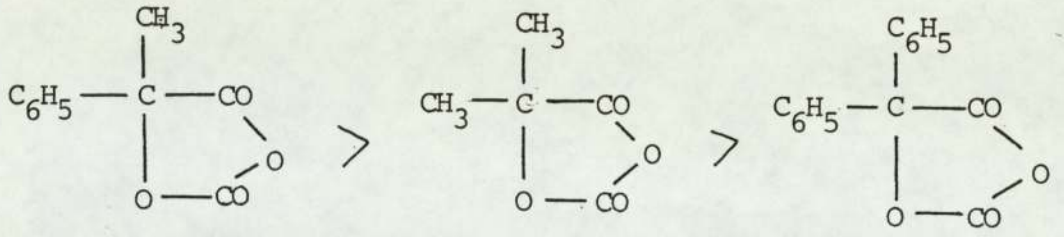
(IX)

the activation of the C(4) carbonyl and the steric hindrance associated with the reaction path. The kinetic parameters are consistent with the proposed mechanism,(Equation 3.3). The activation energy is lower than that required for decomposition of the unactivated ring and supports the idea of the formation of activated intermediate complex. The frequency factor,in the range of 10^{6} - 10^{11} l. mol^{-1}. $sec.^{-1}$, is consistent with a mechanism which is sterically difficult such as the attack of pyridine at the C(4) carbonyl. The negative values of entropy of activation require the formation of a polar transition state. Thus the decomposition of

α - hydroxy anhydrocarboxylate with pyridine exhibits reactivity in the order as shown below:



GAAC MAAC PFAAC



AAAC DMAC BAAC

The value of activation energy (E) for DMAC is somewhat higher than that obtained for the other anhydrocarboxylates and is approximately equal to that for BAAC. The value of frequency factor A (higher) and $\Delta S^{\ddagger}$ (more nearly positive) for these two monomers reflect a more random collisional process and a more hindered approach to the C(4) carbonyl.

The presence of two methyl groups in DMAC presents considerable steric hindrance to an incoming nucleophile. Since the methyl group is an electron donating substituent, in DMAC we have unusual situation of deactivation by the methyl group and in addition the methyl group presents a degree of steric hindrance to nucleophilic attack. This is reflected in the low rate constant for DMAC polymerisation relative to those for other anhydrocarboxylates (Table 4.1)

The effect of initiator structure has been examined, and in particular , the effect of using tertiary bases that are more sterically hindered than pyridine, [2 - methyl pyridine (α - picoline) and 2, 6 - dimethyl pyridine (2, 6 lutidine)]. These were used as initiators for the decomposition of DMAC (Table 3.3) and the other anhydrocarboxylates (Table 4.4) in nitrobenzene , which was selected as a solvent because of

the good kinetic behaviour of polymerisation observed in this solvent. The results shown in Table (4.4) demonstrate that the reaction rates were of the order expected from the steric and electronic factors associated with these initiators. The lone pair of electrons on the nitrogen provide the nucleophilic character to attack the anhydrocarboxylate ring and it would be assumed that the addition of methyl group to the pyridine ring would serve to shield the lone pair of electrons. However, methyl groups also show

Table (4.4)

Monomer	Pyridine k_2 (l. mol^{-1} s^{-1})	∝- Picoline k_2 ($l.mol^{-1}s^{-1}$)	2,6-Lutidine k_2 ($l.mol^{-1}s^{-1}$)
DMAC (a)	21.10×10^{-5}	9.62×10^{-5}	8.75×10^{-5}
MAAC (b)	1.93×10^{-2}	2.07×10^{-2}	2.33×10^{-2}

a) Temperature = 59°C
b) Temperature = 25.8°C (90)

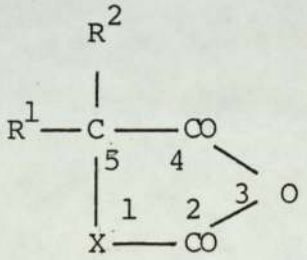
electron donating character and it is therefore reasonable to assume that the nucleophilicity of the attacking species would be increased by the addition of these methyl groups.

The distinction between the basicity and nucleophilicity was studied [1,10] in the reaction of tertiary bases with NCA derivatives of ∝ - amino carboxylic acids. It has been shown that the steric hindrance of the tertiary nitrogen atom decreases the nucleophilic power, hence 2,6 - lutidine is the least reactive nucleophile, and pyridine is the most reactive in situations where steric hindrance is important. When these amines were used to initiate NCA polymerisation in dimethylformamide (DMF), it was found that lutidine was the most efficient catalyst and pyridine the least. This provided evidence that the tertiary bases initiate NCA polymerisation

by proton abstraction (Equation 1.10) and not by nucleophilic attack at the ring carbonyl of the NCA molecule.

The work carried out with DMAC allows direct comparison of anhydrocarboxylate and anhydrosulphite rings to be drawn. Polymerisation of both monomers demonstrated that whereas the pyridine initiated polymerisation of 5, 5 - dimethyl α - hydroxy acid anhydrocarboxylate produced molecular weights in the order of only 2000, thermal polymerisation of 5,5 - dimethyl α - hydroxy acid anhydrosulphite (HBAS) produced polymer having molecular weight in excess of 100,000[78]. It has been shown that addition of pyridine to this anhydrosulphite above room temperature produces rapid decomposition with the formation of products which include low molecular weight polymer[77]. At this point it is emphasised that because of the acidic nature of the anhydrosulphite monomer and especially that of its gasous decomposition product (sulphur dioxide), comparative studies of anhydrocarboxylates and anhydrosulphites with tertiary bases are not possible.

In the polymerisation of anhydrocarboxylates by pyridine, the nature of the heteroatom, (X), plays an important role in determining the rate and nature of the reaction.



(XVI)

As C(5) is directly bonded to the reaction site C(4), it

will also play a significant part. However, the fourth substituent at C (5), namely (X) will make a contribution to both determination of the reaction path and activation (for example by electron withdrawal) of the C(4) carbonyl. The kinetic parameters obtained from pyridine decomposition of the dimethyl substituted anhydrocarboxylate of an α - hydroxy acid DMAC (XVI, $R^1 = R^2 = CH_3$, X =O) are quite similar to that obtained from dimethyl substituted anhydrocarboxylate of an α - thio acid [28] (TIBAC) ($R^1 = R^2 = CH_3$, X = S).

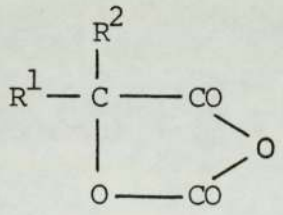
Monomer	Ea K.J. mol^{-1}	A 1. $mol.^{-1} Sec.^{-1}$	$\Delta S^{\ddagger}$ J. K^{-1} mol^{-1}
DMAC	82.6	5.8×10^8	- 76.9
TIBAC	55.2	6.0×10^8	- 65.6

Lower molecular weight polymer was obtained from TIBAC with pyridine compared with that from DMAC with pyridine however.

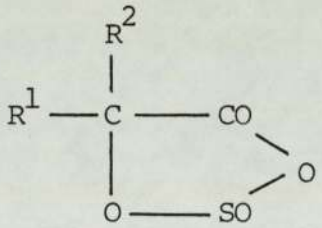
Previous study [28] has shown that the mechanism of the reaction between pyridine and thio - anhydrocarboxylates is analogous to the attack of this initiator on the anhydrocarboxylates of the corresponding α - hydroxy acids. The presence of the sulphur atom renders the ring more reactive than the corresponding oxygen containing ring, and with protonic initiation the thiol group $\sim$SH generated is more nucleophilic in the propagation step than the hydroxyl group. The relative reactivity of DMAC and TIBAC can be understood from the thermal decomposition of these monomers. The rate constant value for TIBAC is 8.6×10^{-6} $sec.^{-1}$ at $90^{\circ}C$ and is eighty times faster than the analagous value for DMAC. This is due to the fact that sulphur being a larger atom than oxygen causes more ring

strain. Similarly the relative values for decomposition of DMAC and TIBAC in the presence of pyridine at 50°c in nitrobenzene are 12.6×10^{-5} $l.mol^{-1}sec^{-1}$ and 8.0×10^{-3} $l.\ mol^{-1}sec^{-1}$ (approx.) this probably reflects the faster rate of decomposition of the pyridine complex with the more highly strained sulphur - containing ring.

Finally, it is interesting to examine the role of pyridine as a novel initiator to enable more equal copolymerisation of monomer pairs such as anhydrocarboxylate (IX) and anhydrosulphites (VIII) to be achieved. Mechanistic studies of this type are useful in order to attempt to increase the understanding and versatility of this type of polymerisation which is of considerable potential value in view of the current biomedical interest in biodegradable poly - α - esters



(IX)



(VIII)

In the copolymerisation of anhydrocarboxylates, the reactivity of the individual monomer with pyridine is obviously important From Table (4.2), the reactivity of anhydrocarboxylate mainly depends on the substituents R^1 and R^2.

Since the rate determining step in these polymerisations is the production of the reactive α-lactone intermediate, the first-order rate constant for monomer decomposition at a given pyridine concentration represents the rate of incorporation of that lactone into the polymer. Blackbourn [101] has studied the copolymerisation reaction involving α - lactones and shown that rate of incorporation for two monomers M_1 and M_2 is given by

$$-\frac{d[M_1]}{dt} = k_1[M_1]$$

$$-\frac{d[M_2]}{dt} = k_2[M_2]$$

Thus if R_1 and R_2 are very different it is difficult to achieve a reasonable range of copolymerisation compositions.

Copolymerisation of anhydrocarboxylates with anhydrosulphites using pyridine as initiator presents problems. The thermal stability of these monomers has been explained in terms of the relative size of carbon and sulphur in the 2 - position being very different. It is known that the anhydrosulphites are very reactive with pyridine (even at room temperature) yielding only low molecular weight polymer. As the role of pyridine in the copolymerisation of anhydrocarboxylate and anhydrosulphite is to control the rate of reaction, it is probable that all the anhydrosulphite monomer would disappear before any appreciable amount of anhydrocarboxylate would react. This study hopefully might enable some alternative initiator system to overcome the problems to be developed. Varying the structure of pyridine plays an important role in the explanation of the tertiary bases' behaviour towards anhydrocarboxylates for example by using sterically hindered base(for example 2-methyl pyridine

and 2,6 dimethyl pyridine). Because of the balance of the two factors; steric and polar there is an increase in the rate of reaction in case of MAAC ie. in the following order

2,6 dimethyl-pyridine > 2-methyl pyridine > pyridine

which demonstrates that as the nucleophilicity of the nitrogen increased, the rate of reaction is increased. With disubstituted monomers however eg. BAAC, DMAC the rate of decomposition with 2-methyl pyridine and 2,6-lutidine was slower than with pyridine. From these observations, it is apparent that the effect of steric effects in the attacking tertiary base is more important in the case of DMAC and BAAC than the electronic effect, while the reverse situation is found in case of MAAC. The effect is governed by the steric hindrance imposed by the C(5) substituent of the monomer ring. Thus in the case of MAAC, tertiary base attack for one side of the ring is virtually unhindered. The effect of replacing the C (5) substituents by two methyl or two phenyl groups is to sterically impair the attack of the incoming tertiary base from both sides of the ring.

It is possible that this information will enable some progress to be made in controlled polymerisation of various monomer pairs. One possible approach is the use of supported tertiary base catalysts. Some preliminary results in this area are presented in chapter 7.

CHAPTER 5

Kinetic Studies of the Alkoxide Initiated Decomposition of Anhydrosulphites and Anhydrocarboxylates.

Initiated polymerisation of cyclic esters has many advantages over thermal polymerisation which frequently requires high temperature as, for example, in the thermal decomposition of anhydrocarboxylates. The aim of this study is to compare the reactivity of anhydrocarboxylates and anhydrosulphites using an initiator of anionic character, for example, lithium tertiary butoxide. As with the work described in chapter 3 and 4, the main reason for carrying out this work is to provide some comparative basis upon which initiators for copolymerisation may be selected.

Comparison between anhydrocarboxylates and anhydrosulphites with more basic initiators such as pyridine is difficult, however, due to the high reactivity of pyridine with anhydrosulphites and the nature of the product.

The use of alkoxides in anhydrosulphite polymerisation has been reported previously and some examination of the reaction of disubstituted anhydrosulphites with lithium tertiary butoxide has been carried out by Crowe[93]. In this chapter the anhydrocarboxylates GAAC, DMAC (IX; $R^1=R^2=H$, $R^1=R^2=CH_3$) are compared in reactivity to GAAS (VIII, $R^1=R^2=H$) and also with the disubstituted anhydrosulphites studied by Crowe. Although other alkoxides were examined by Crowe, lithium tertiary butoxide was found to give best results on account of its improved solubility behaviour in comparison with

eg. sodium methoxide.

5.1 Decomposition of Glycollic Acid Anhydrocarboxylate by Lithium tertiary butoxide .

Glycollic acid anhydrocarboxylate was prepared and purified as described in chapter 2. The solutions of the monomer and the catalyst were prepared in the dry box under dry inert atmosphere.

The rate of decomposition was studied by gas evolution techniques using apparatus which is shown in Figure (2.3). Figure (5.1) shows the reaction profile of pressure rise Pt/P_{∞} versus time for the system GAAC /lithium tertiary butoxide / toluene . A conventional first order plot of log $\frac{[M]}{[M]_o}$ Vs time gave non-linear behaviour. A typical first order plot is shown in Figure (5.2). Although a straight line could conceivably be seen for the first 40 - 50% of the reaction, the reaction thereafter proceeds increasingly slowly and clearly does not proceed with first order kinetics with respect to monomer through the complete reaction.

The possibility that a second - order kinetic analysis might more closely fit the experimental results was always borne in mind. Although it is difficult to choose between two imperfect alternatives the second order plot did not appear to offer any help in the interpretation. Figure (5.3) shows a plot of this type in which the experimental results of Figures (5.1) and (5.2) are analysed in the form of a second order plot.

The sigmoidal shape showing acceleration towards the end of the reaction as well as a very fast initial rate is difficult to reconcile with the reactions studied here and

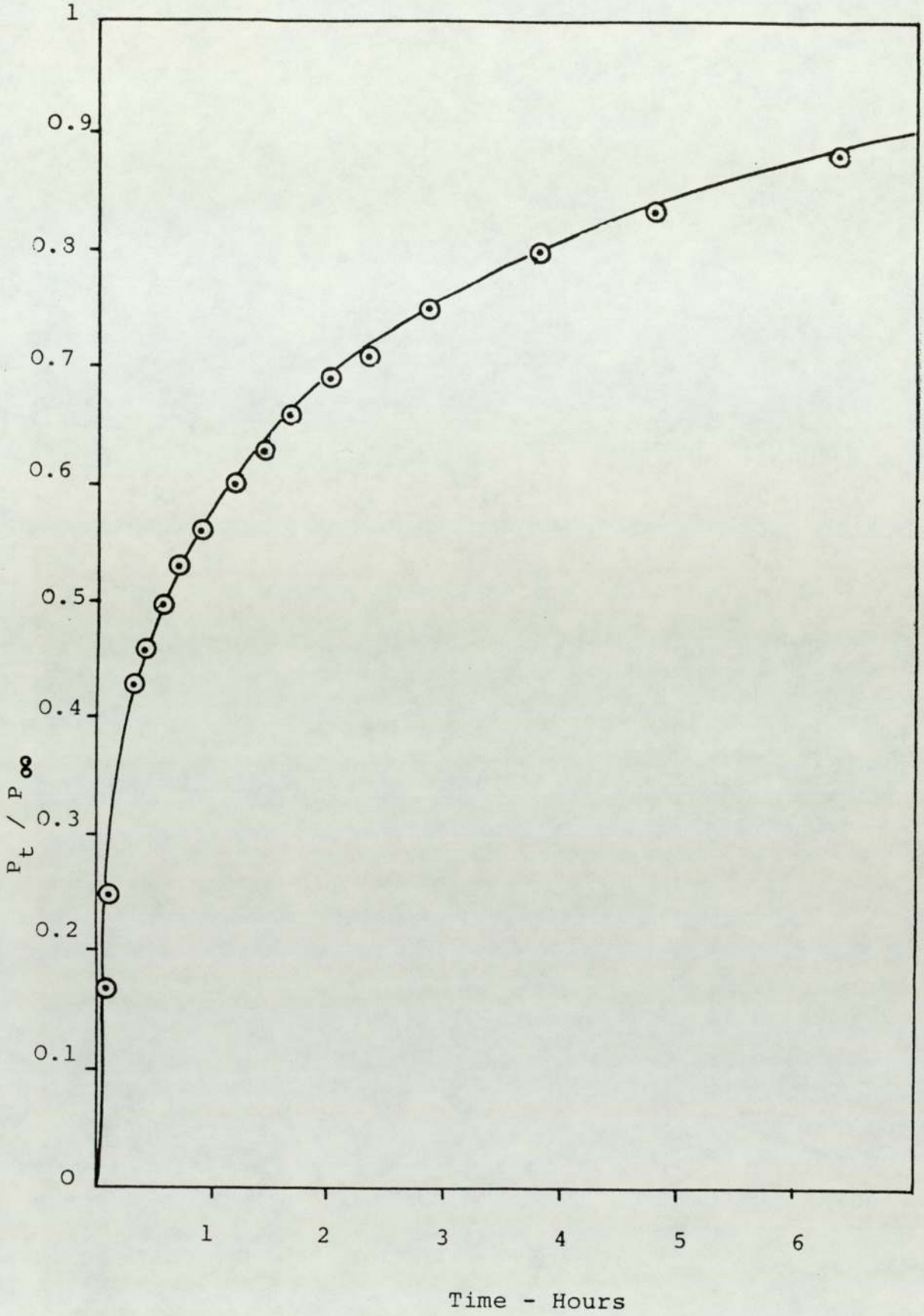


Figure 5.1 Decomposition of GAAC in the presence of lithium tertiary butoxide using toluene as solvent at 30°C.

$[GAAC]_o = 0.50$ M

$[LiO_t\ C_4H_9]_o = 0.027$ M

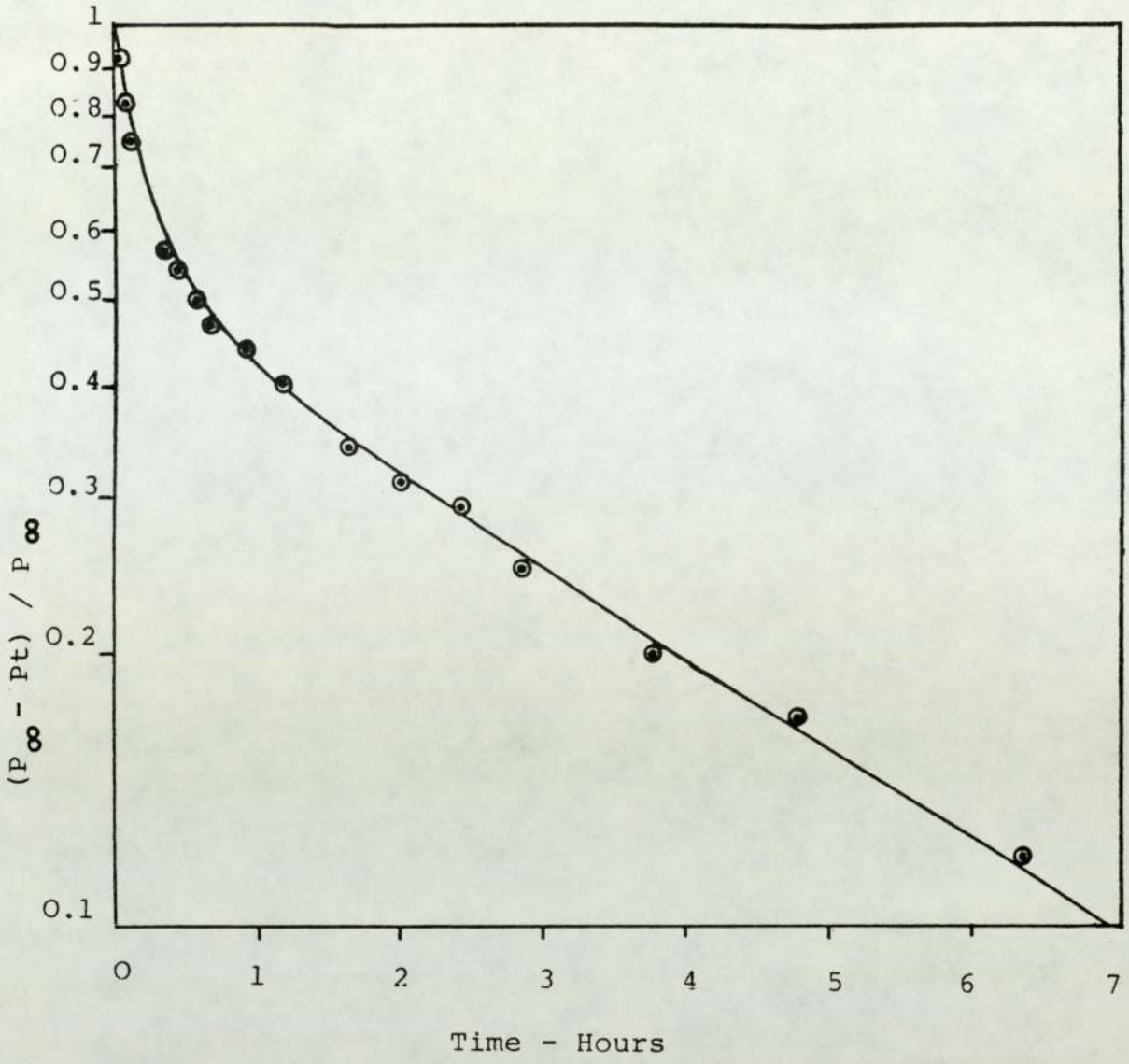


Figure 5.2 First-order plot of decomposition of GAAC in the presence of lithium t - butoxide in toluene as solvent at 30°C.

$$\left[GAAC\right]_o = 0.50 \text{ M}$$

$$\left[LiO_t\ C_4\ H_9\right]_o = 0.027 \text{ M}$$

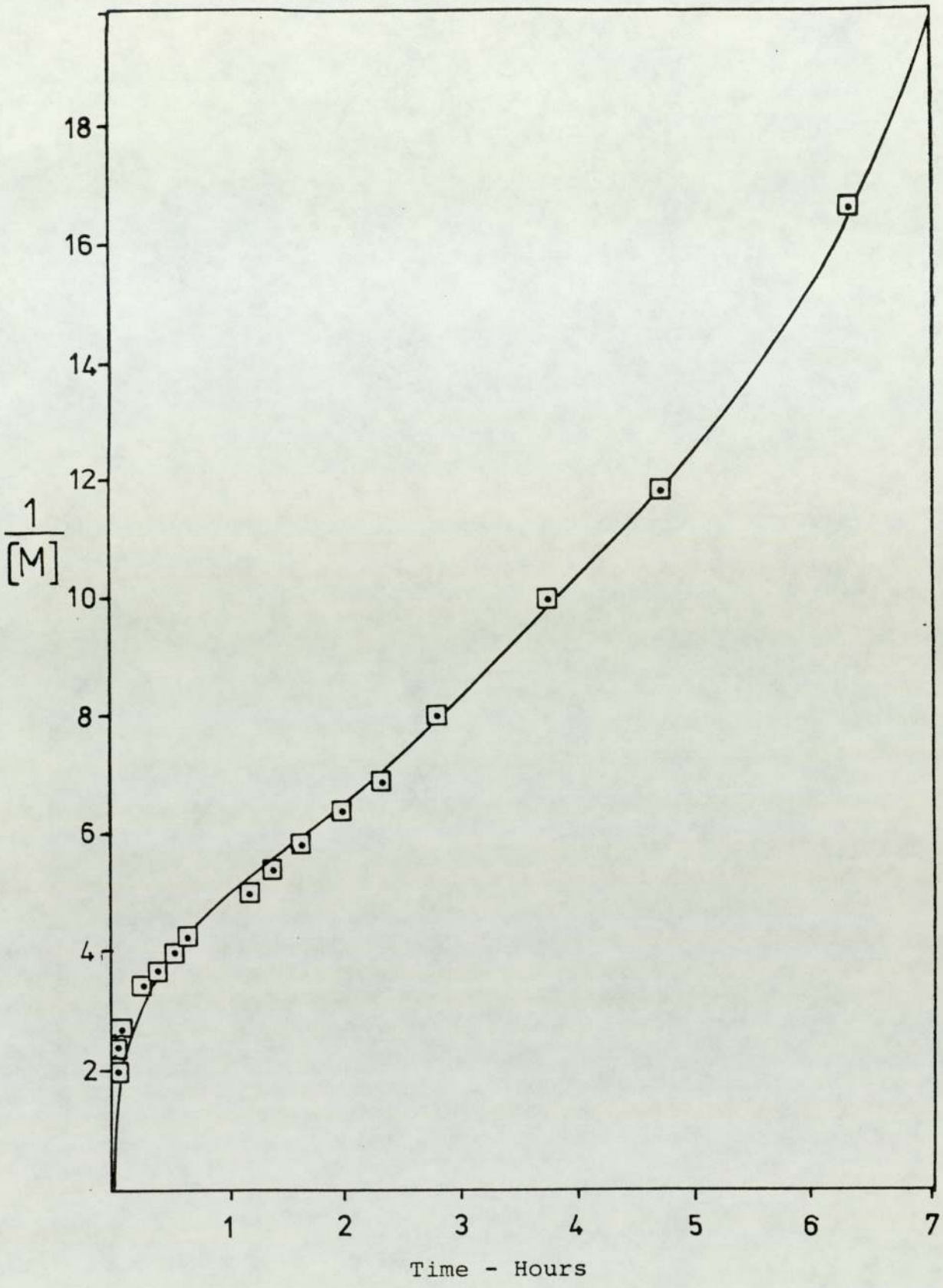


Figure 5.3 Second order plot of decomposition of GAAC in the presence of lithium t - butoxide in toluene as solvent at 30°C

$[GAAC]_o = 0.50$ M

$[LiO_tC_4H_9]_o = 0.027$ M

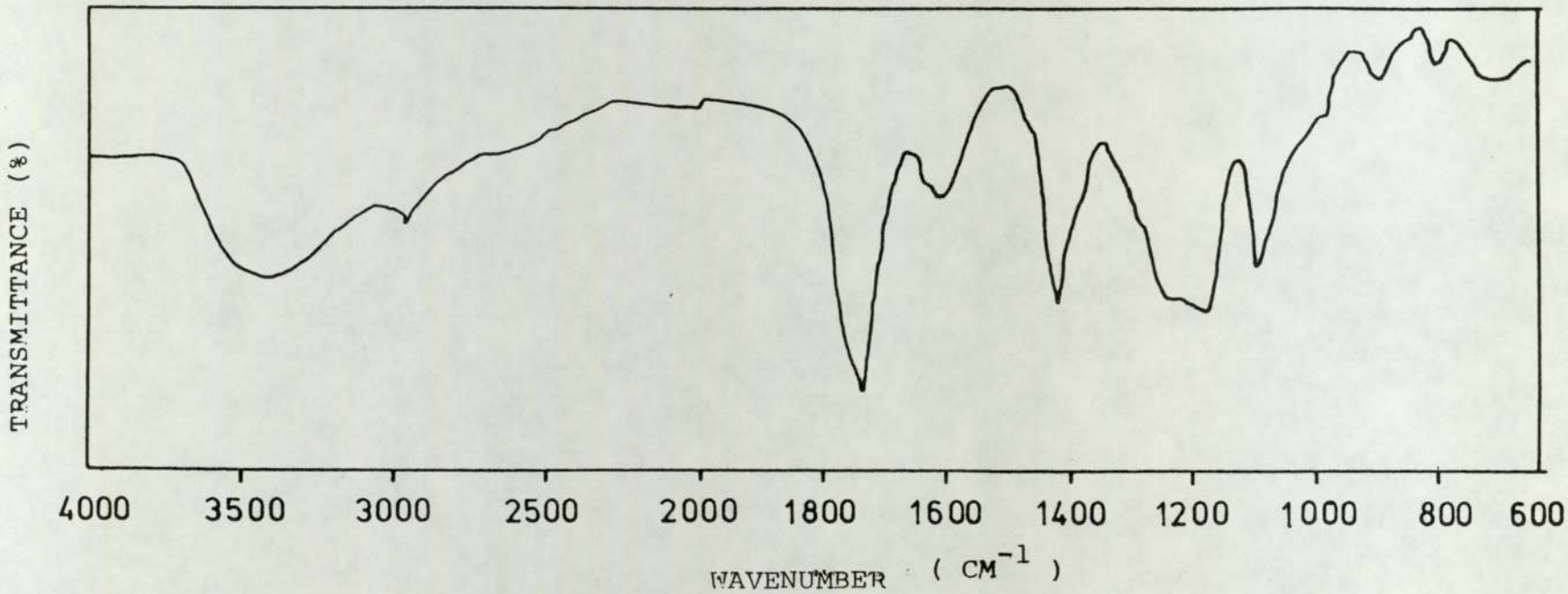
particularly with the observed heterogeneity. The possibility of second order behaviour contributing to a complex mechanism could not, however, be entirely ruled out.

One obvious difference between these reactions and those in which good first order behaviour is observed (eg. thermal polymerisation of anhydrosulphites, pyridine initiated decomposition of anhydrocarboxylate) lies in the fact that the GAAC/ Lithium tertiary butoxide reaction was observed to become heterogeneous during the course of the reaction. The onset of the heterogeneity corresponds fairly exactly with deviation from simple first order behaviour and is first observed at about 50% decomposition.

Product Characterisation

Lithium tertiary butoxide does not have a high solubility in toluene but even in the presence of solid undisssolved alkoxide, the glycollic acid anhydrocarboxylate is decomposed at an appreciable rate to yield a product which appears to be a poly - α - ester. After the reaction is completed, two layers were separated, a liquid layer (upper layer) which after being withdrawn, was examined by ir spectroscopy which indicated that this layer is pure solvent. The second layer (the product) was subjected to vacuum to remove the traces of solvent and the white solid produced was washed with ether. The melting point of the product was 175^{o}C, and infra - red analysis which is shown in Figure (5.4) yielded two carbonyl absorptions. The strong absorption peak at 1740 cm^{-1} corresponds to the carbonyl stretching frequency in the polymer. In addition a further absorption was noted at 1620 cm^{-1} which is

Figure 5.4 : Infra-red spectrum of polymeric product obtained from the decomposition of GAAC by lithium t - butoxide in toluene.
KBr disc, reference air.



not shown in the product produced from thermal decomposition of anhydroacrboxylate. In addition to carbonyl peaks, a weak broad absorption around 3500 cm^{-1} was shown in the spectra indicating the presence of hydroxyl groups. This broad peak may be due to the presence of moisture caused by the hygroscopic alkoxide residues.

Effect of Solvent Polarity

In the previous study by Crowe, decalin was used as a solvent in the decomposition of anhydrosulphites with lithium tertiary butoxide. The selection of decalin as a solvent results from the following factors:

(i) Alkoxides derived from Group I elements and having a large alkyl group (eg. lithium tertiary butoxide) are comparatively soluble in non - polar organic solvents like decalin.

(ii) The high boiling point of decalin allows the process of anhydrosulphite decomposition to be followed by gas evolution since the low volatility of this solvent does not cause any interference with the manometric method of following gas evoultion at constant volumes .

In the work described here the monomers used (GAAC, GAAS, DMAC) did not have the same high solubility in decalin as did the dialkyl substituted anhydrosulphites used by Crowe. This placed a restriction on the choice of solvents and solvent mixture. Some changes in solvent polarity were made, however, in order to assess the effect of an increase in solvent polarity on the rate of decomposition of GAAC in the presence of lithium tertiary butoxide as initiator and on the nature of the product.

A typical pressure versus time profile (obtained using the gas evolution technique) in a more polar solvent mixture (nitrobenzene : decalin , 2:1(V/V) is shown in Figure (5.5). Figure (5.6) shows the corresponding first - order plot of log $(P_\infty - Pt) / P_\infty$ Vs time which gives non-linear behaviour similar to that shown in toluene (Figure 5.2). Comparison of Figure (5.2) and (5.6) indicates that the form of the interaction between GAAC and the initiator is not dramatically affected by introducing a polar solvent .

Although the reactions in nitrobenzene / decalin represented by Figure (5.6) were carried out at 40°C (to facilitate comparison with GAAS made in a later section) and the reaction in toluene was carried out at 30°C two conclusions can be drawn. In the first place the non - linear behaviour in both cases is possibly related to the increasing heterogenity of the system. Secondly the reaction in the more polar solvent system proceeded at a noticeably slower rate than that in toluene. If initial rates of the two reactions shown in Figures (5.2) and (5.6) are compared on the basis

$$-\frac{d[M]}{dt} = k_2 [M] [Cat]$$

(this may not be valid but will serve to make this rough comparison) the derived values of k' are :-

k_2 (toluene, 30°C) = 29.6×10^{-4} l. $mol.^{-1}$ $sec.^{-1}$

k_2 (nitrobenzene/decalin, 40°C) = 8.1×10^{-4} $l.mol.^{-1}sec.^{-1}$

this comparison, which undoubtedly reflects on the nature of the reaction will be considered in the later discussion section.

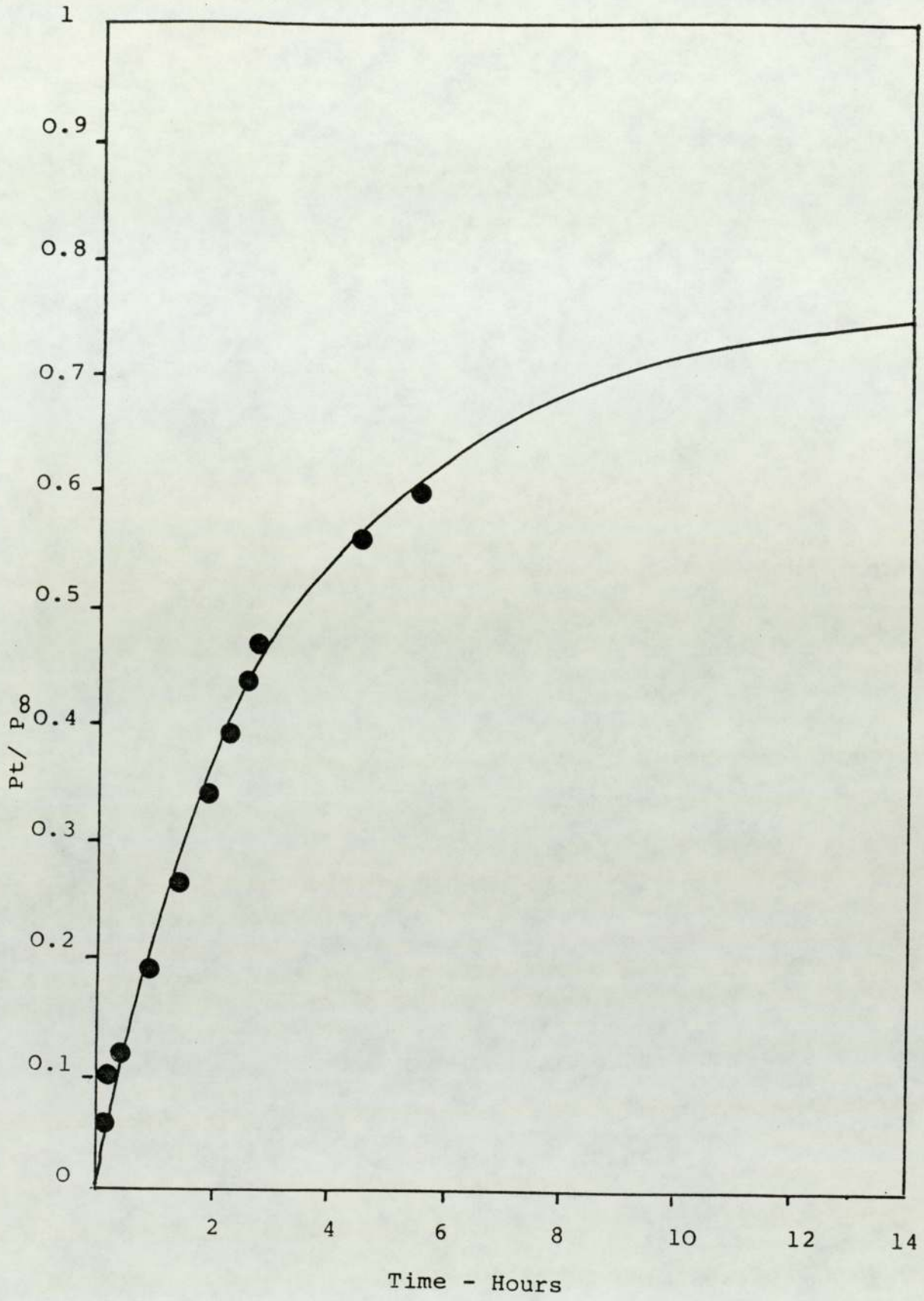


Figure 5.5 Decomposition of GAAC in the presence of lithium t - butoxide at 40°C

$\left[GAAC\right]_o$ = 0.863 M

$\left[LiO_tC_4H_9\right]_o$ = 0.07 M

Solvent Nitrobenzene : Decalin V/V 2 : 1

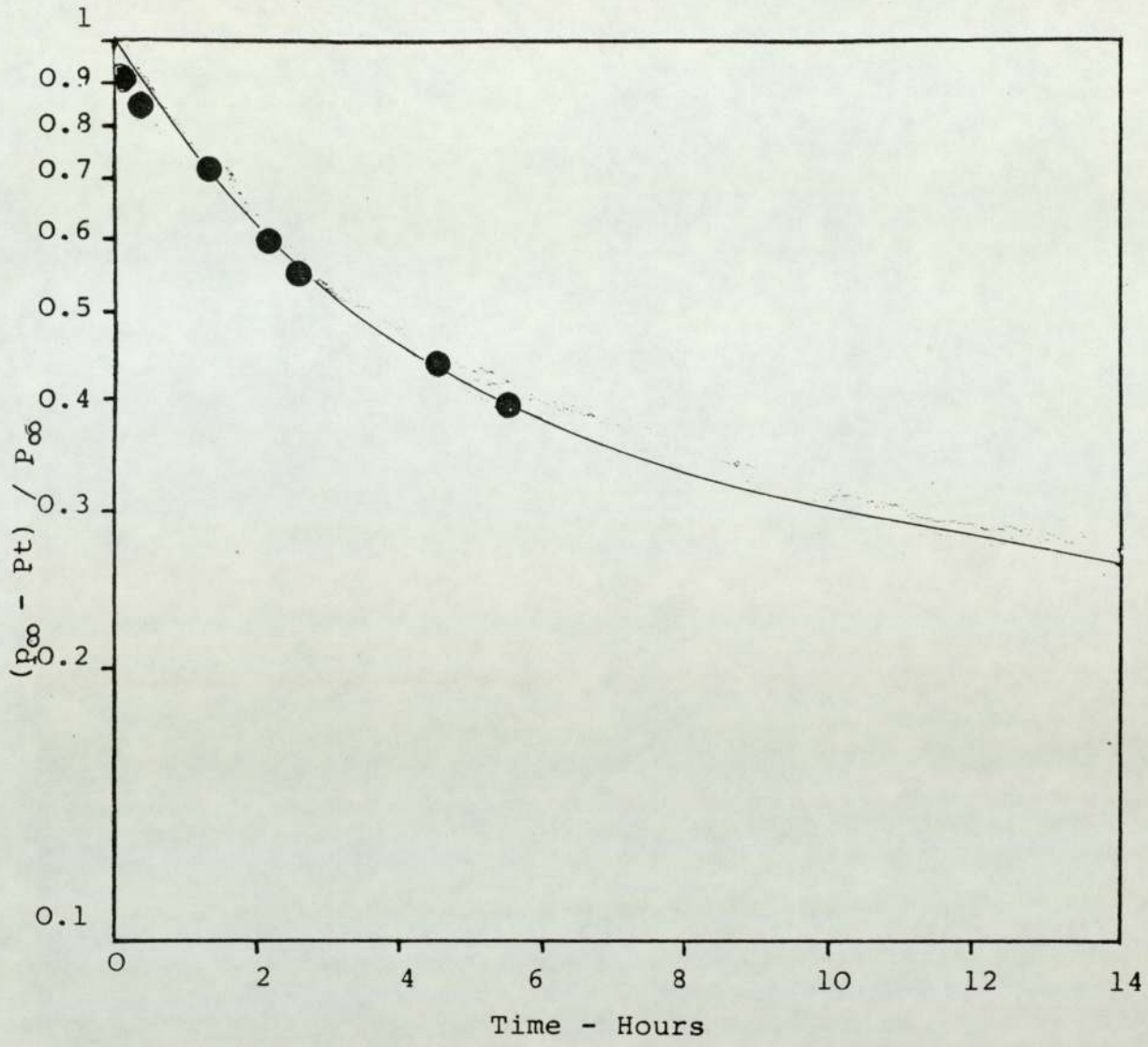


Figure 5.6 First-order plot of decomposition of GAAC in the presence of lithium t - butoxide at 40°C.

$[GAAC]_o$ = 0.863 M

$[LiO_tC_4H_9]_o$ = 0.07 M

Solvent Nitrobenzene : Decalin

2 : 1

Product Characterisation : -

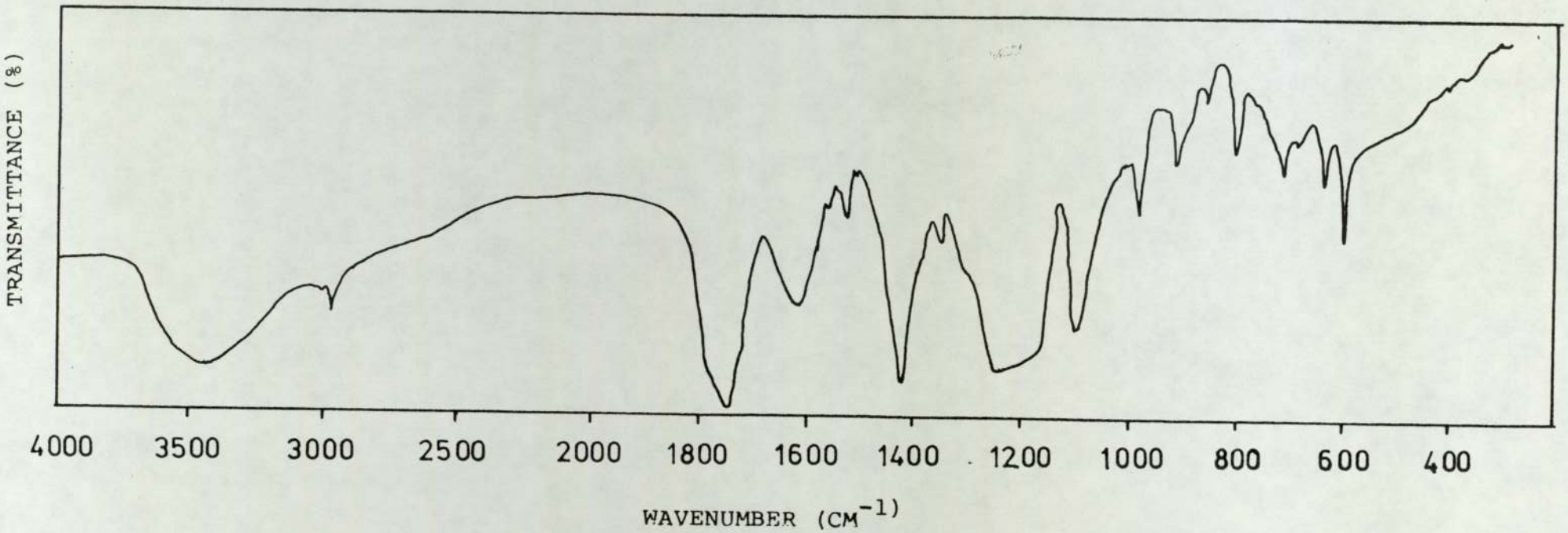
The products were separated by removing the solvents under vacuum at 40°C. The white solid produced was washed with ether and after drying, its infra - red spectrum, (Figure 5.7), was taken. Two absorptions were observed, one at 1740 cm^{-1} (strong) which is typical of the poly - α -ester and the other (medium) at 1620 cm^{-1} which was attributed by Crowe, working with similar compounds, to a non - polymeric metal salt. The total yield of solid product from the reaction represented by Figure (5.2) and (5.6) was similar to Crowe's as was the ratio of metal salt to poly - α - ester

5.2 Decomposition of Glycollic acid anhydrosulphite in the presence of lithium tertiary butoxide.

5.2.1. Kinetic Studies

The experiments were carried out using the apparatus of type shown in Figure (2.4). In view of the poor solubility of GAAS in decalin, which is otherwise an excellent solvent for the catalyst, certain other solvents were examined. Whilst the monomer is soluble in both nitrobenzene and anisole, both solvents proved to be unsuitable for the catalyst study. It was decided to use nitrobenzene as solvent for the monomer and decalin as a solvent for the catalyst since both components remained soluble in the mixed solvent. In order to obtain consistently repeatable results the reaction mixture required vigorous and repeated agitation. This presumably results from the increased solubility of sulphur dioxide in organic solvents

Figure 5.7 Infra-red spectrum of polymeric product obtained from the decomposition of GAAC by lithium t - butoxide at 40°C solvent Nitrobenzene: Decalin (2:1). KBr disc, reference air.



at lower temperature than those used in thermal decomposition, the reaction solvents being easily supersaturated.

The rate of evolution of sulphur dioxide at 40°C was measured by observing the manometric pressure rise at constant volume. Solutions of the monomer in nitrobenzene and lithium tertiary butoxide in decalin were prepared in the dry box. The reaction profiles of decomposition of GAAS with different $[M]_o/[I]_o$ and solvent ratios are shown in Figure (5.8). Table (5.1) shows the derived second-order rate constant for the decomposition of GAAS with lithium tertiary butoxide using decalin/nitrobenzene co-solvents in various proportions.

Table 5.1

Second order rate constants for the decomposition of GAAS in the presence of lithium t - butoxide at 40°C using various decalin / nitrobenzene co -solvent mixtures.

$[M]_o$ mol l^{-1}	$[I]_o$ mol l^{-1}	$\frac{[M]_o}{[I]_o}$	Solvent ratio V/V		k_2 10^{-4} $l.mol^{-1}$ sec^{-1}
			Nitrobenzene	Decalin	
0.60	0.053	11.3	1.5	1.5	11.0
0.60	0.109	5.5	1.5	1.5	7.35
0.79	0.035	22.6	2	1	6.6
0.79	0.0729	10.8	2	1	7.32

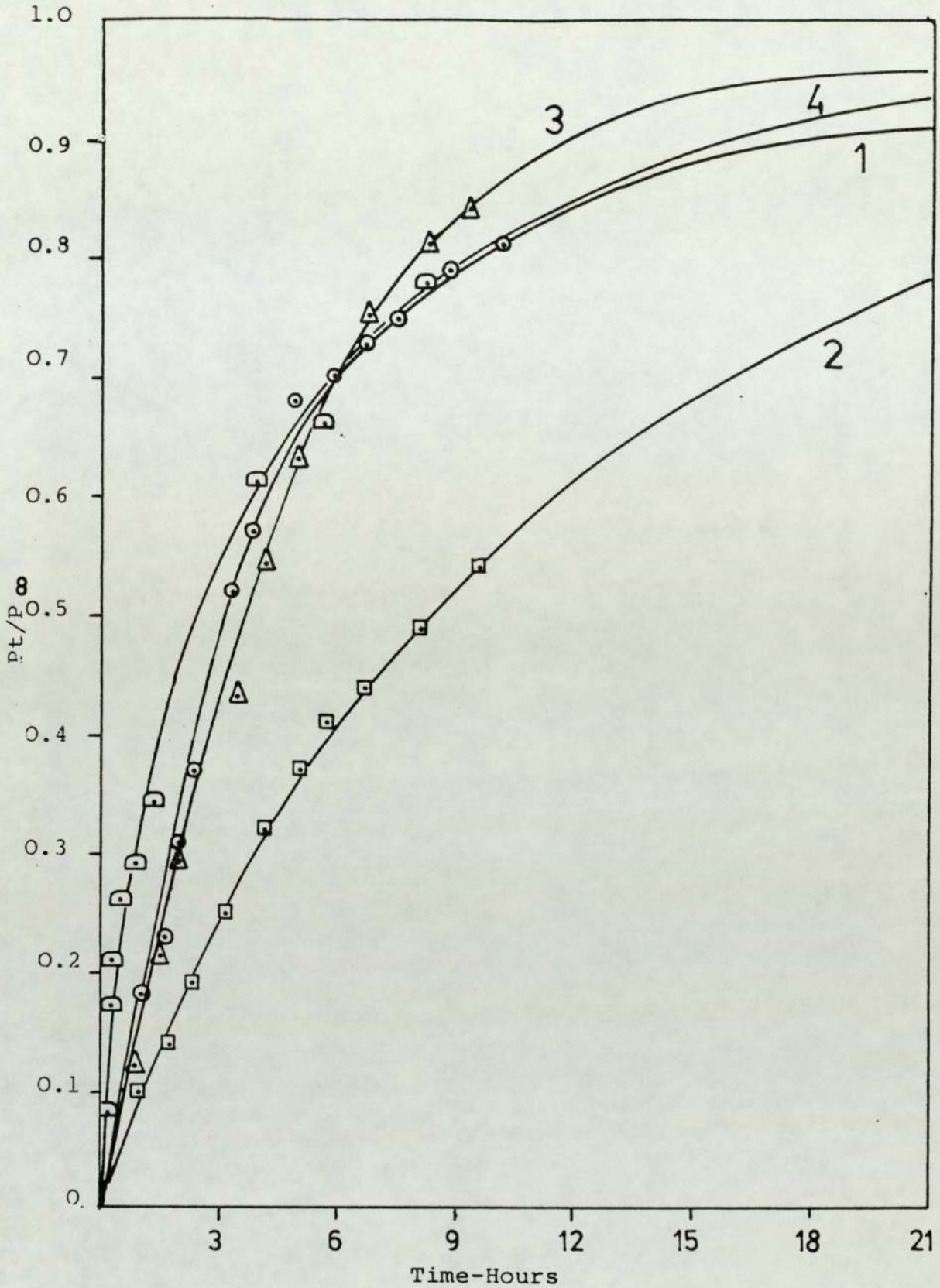


Figure 5.8

Decomposition of GAAS in the presence of lithium t- butoxide at 40°C.

○ (1) $[M]_o / [I]$ = 11.3 , Nitrobenzene:Decalin =1.5:1.5 (V/V)

□ (2) $[M]_o / [I]$ = 22.6 , Nitrobenzene:Decalin = 2:1(V/V)

△ (3) $[M]_o / [I]$ = 10.8 , Nitrobenzene:Decalin = 2:1(V/V)

⊐ (4) $[M]_o / [I]$ = 5.4 , Nitrobenzene:Decalin = 1.5:1.5 (V/V)

In one experiment, toluene was used as solvent in the decomposition of GAAS ($[M]_o$ = 0.60 mol.l.$^{-1}$) with lithium tertiary butoxide ($[I]_o$ = 0.0125 mol.l.$^{-1}$) at 30°C. The reaction was very slow, and a white gel was formed.

5.2.2 Characterisation of product from GAAS reacted with Lithium tertiary butoxide

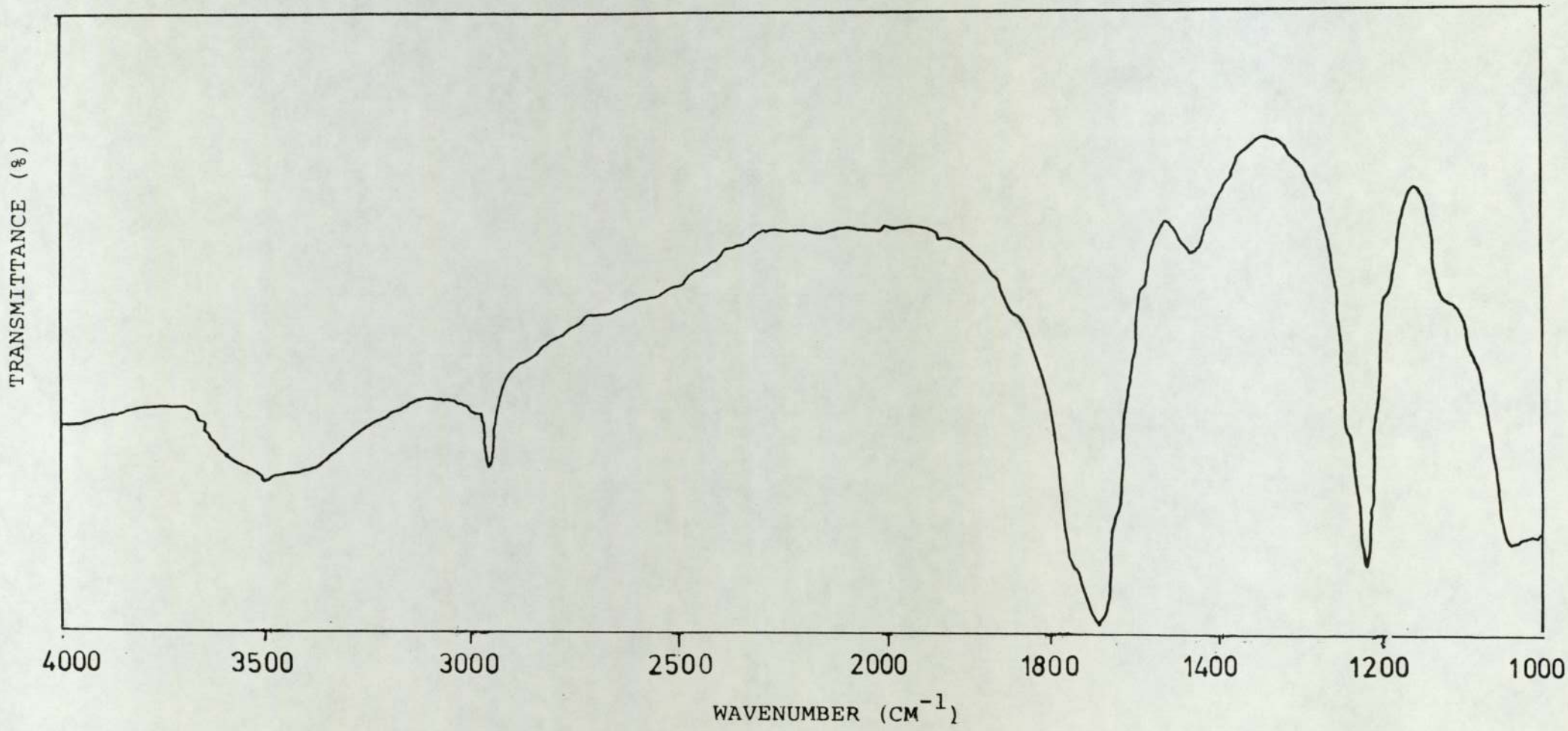
In order to study the nature of the product which was produced from the decomposition of GAAS with lithium tertiary butoxide, a bulk polymerisation experiment was carried out using decalin as solvent, in spite of the poor solubility of GAAS in decalin. Preparation of the product was carried out under reduced pressure by using a carius tube which is described in chapter 2, Figure (2.5). The ratio of monomer to initiator $[M]_o / [I]_o$ is 82 at 40°C. The white gel which is formed at the end of the experiment was treated under vacuum to remove the traces of the solvent . Finally the white solid was washed with ether and after drying, the melting point was found to be 135°C. Infra - red analysis (Figure 5.9) shows a strong absorption at 1740 cm^{-1} and a smaller peak at 1620 cm^{-1}. These peaks are typical of poly - α - ester and metal salt (see section 5.5).

5.3 Lithium tertiary butoxide initiated decomposition of Dimethyl anhydrocarboxylate DMAC.

It has already been established that lithium tertiary butoxide is a good catalyst for the polymerisation of some cyclic monomers, for example the anhydrosulphites. The initiated decomposition of anhydrocarboxylates at temperatures below

Figure 5.9

Infra-red spectrum of polymeric product obtained from the decomposition of GAAS by lithium t- butoxide at 40°C in decalin, KBr disc, reference air.



that required for thermal decomposition have been little studied, excepting the work by Smith [57] and the work which is presented in this thesis (Chapter 3). A problem exists in understanding the results of one previous worker [105] who was unable to polymerise dimethyl anhydrocarboxylate however. This may be due to the purity of solvent and alkoxide used and it would be advantageous to study this effect with more detail in this chapter.

Attempts to polymerise anhydrocarboxylates in the region of room temperature using lithium tertiary butoxide have met with varying degrees of success depending upon the monomer structure and nature of solvent. In the present work, decalin was used as a solvent, but there is difficulty in studying the kinetics of the polymerisation, since the DMAC monomer dissolved only with difficulty in decalin. The maximum solubility was required from the monomer, since in a heterogenous system it is almost invariably more difficult to analyse the kinetic results. More effective solvents for the monomer unfortunately tend to deactivate the initiator.

The decomposition of DMAC in the presence of lithium t - butoxide using decalin / nitrobenzene co -solvent mixture was briefly studied at 40°C and 50°C. A monomer concentration of 0.664 mol. $l.^{-1}$ and a lithium t - butoxide concentration of 0.0515 mol. $l.^{-1}$ were used. The reaction profiles are shown in Figure (5.10) indicating the effect of temperature on reaction rate. Infra red analysis of the product was made after the bulk of the solvent had been removed and the spectrum obtained is shown in Figure (5.15).

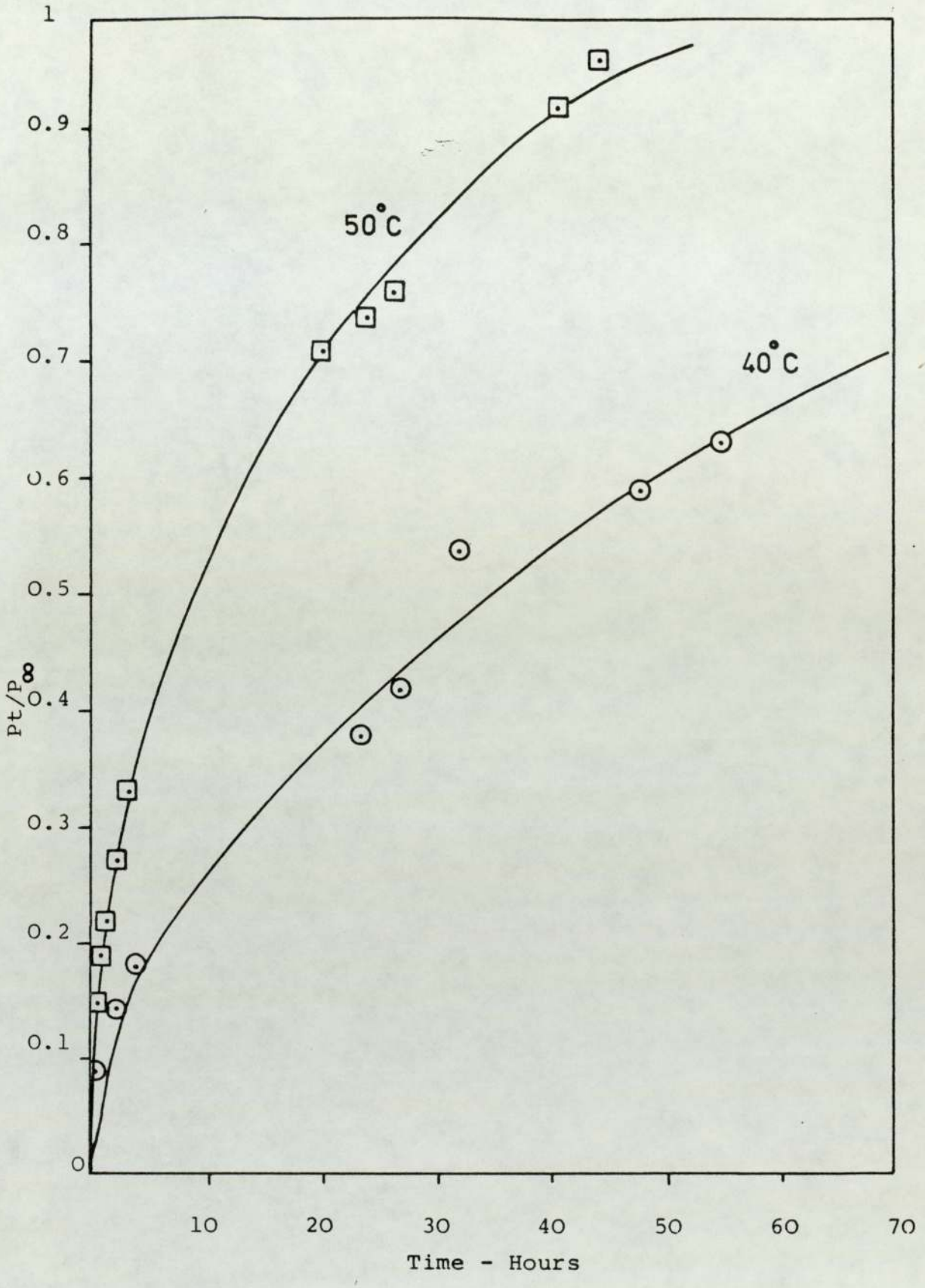


Figure 5.10 Decomposition of DMAC in the presence of lithium t- butoxide in Nitrobenzene / Decalin co-solvent

$[DMAC]_o = 0.664$ M

$[LiO_tC_4H_9]_o = 0.0515$ M

Dimethyl sulphoxide (DMSO) was also used as a solvent because it is a good solvent for the monomer and lithium tertiary butoxide. Figure (5.11) shows the effect of the lithium tertiary butoxide / dimethyl sulphoxide system on DMAC. The reaction was fast in the beginning and then became slow in the latter stages. A first - order plot of log $(P_\infty - Pt) / P_\infty$ Vs time was non -linear and is shown in Figure (5.12). Another experiment was carried out in the absence of lithium tertiary butoxide ie. thermal decomposition of DMAC in DMSO as solvent and Figure (5.13) shows the first order plot. From this experiment it was suggested that DMSO has an activity that enhances the decomposition of DMAC. Infra red analysis of the solution from decomposition of DMAC with lithium tertiary butoxide in DMSO as a solvent shows a strong peak at 1740 cm^{-1} which indicates that the product is probably a poly - α - ester which is soluble in DMSO.

5.4 Decomposition of DMAC in the presence of sodium methoxide

Decomposition of DMAC using sodium methoxide was studied briefly. A temperature of 40^{o}C was used with nitrobenzene as a solvent. In the system sodium methoxide / nitrobenzene, the catalyst was not completely soluble and the decomposition of the monomer was very slow and no product was isolated. The reaction between DMAC and sodium methoxide was followed by using infra red absorption using the apparatus shown in Figure (2.6) under inert atmosphere. Again, the products from the reaction are unchanged monomer and sodium methoxide.

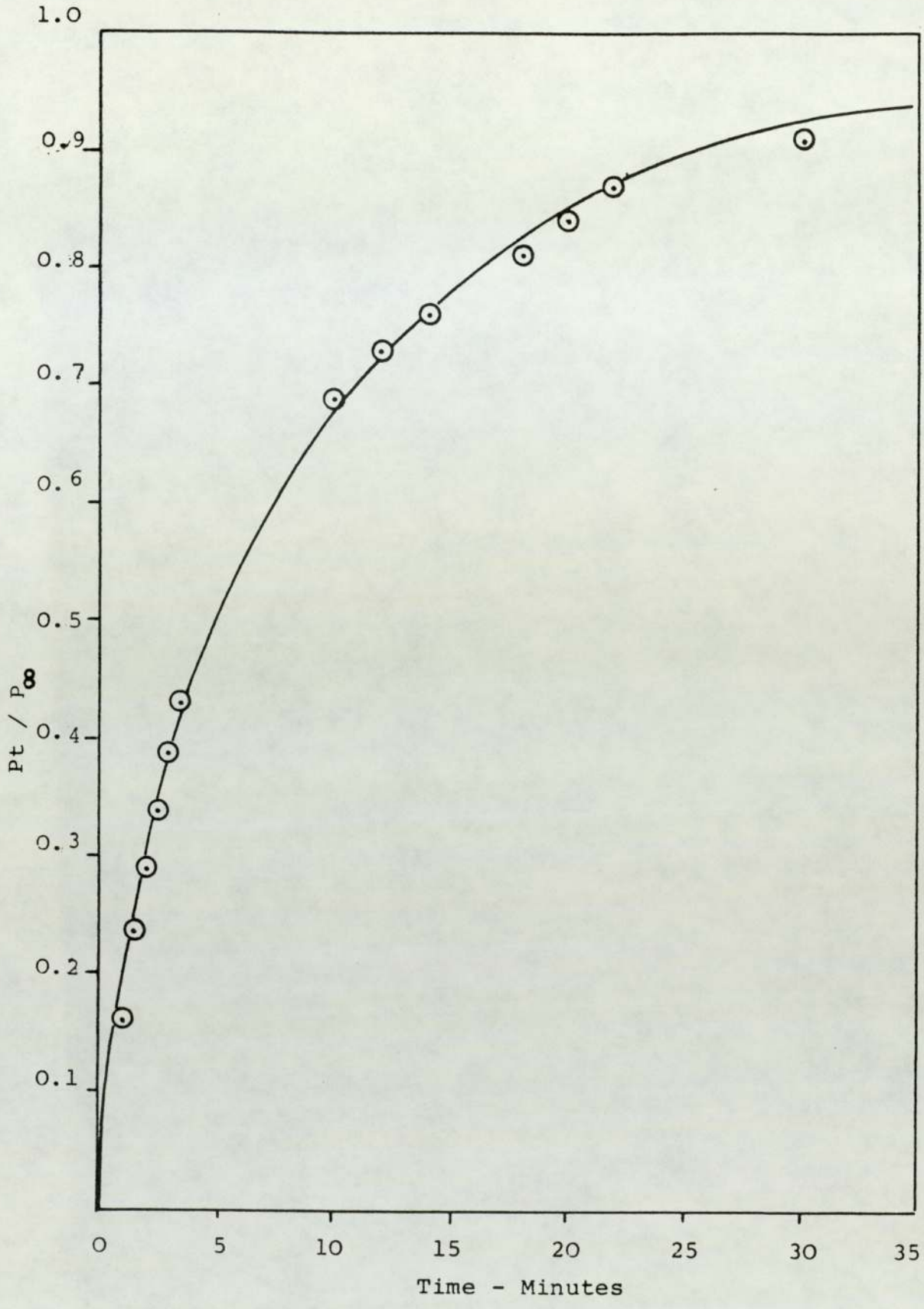


Figure 5.11

Decomposition of DMAC t - butoxide at 40°C in Dimethyl Sulphoxide as solvent

$\left[DMAC\right]_o$ = 0.97 M

$\left[LiO_tC_4H_9\right]_o$ = 0.10 M

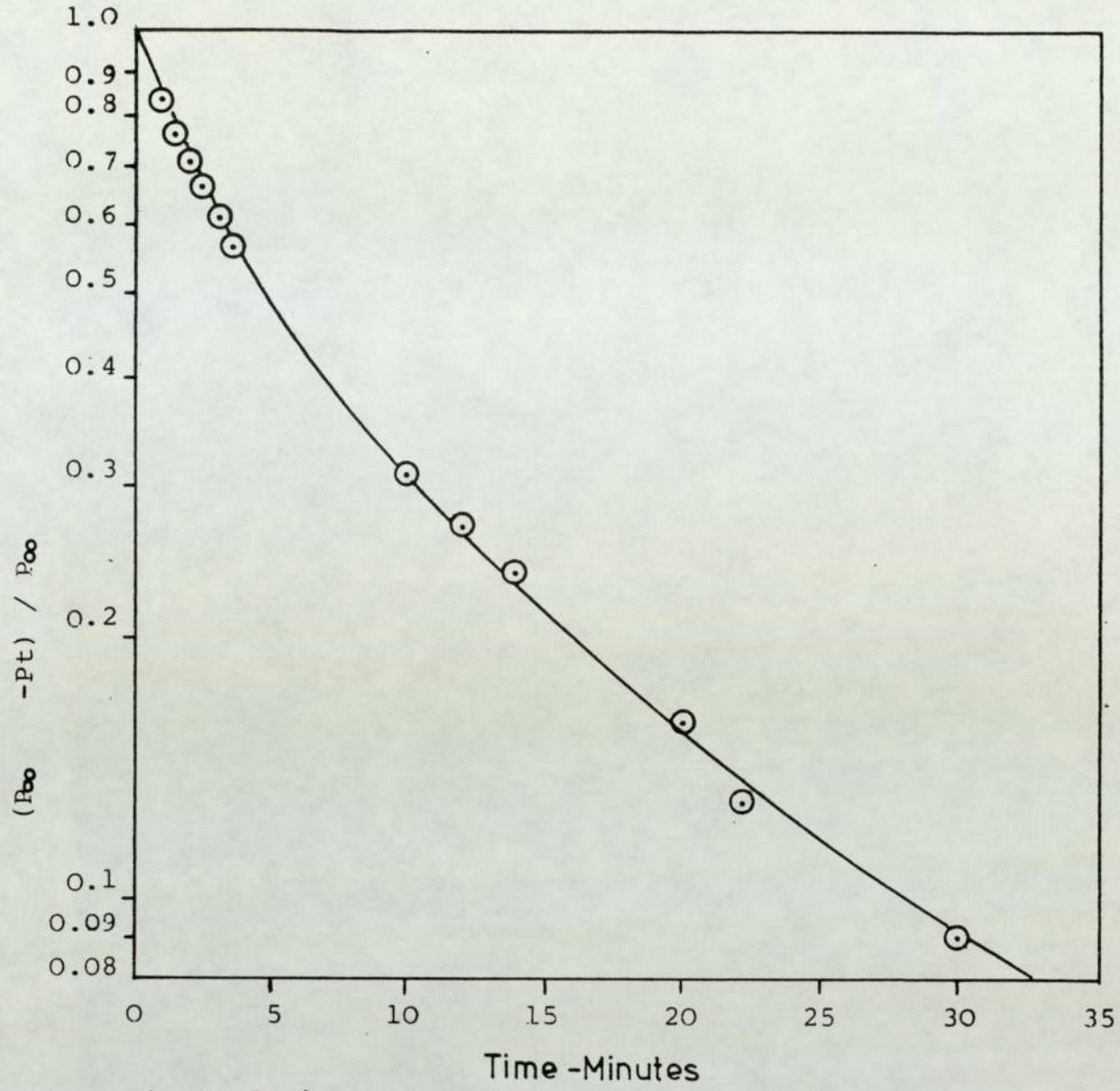


Figure 5.12

First-order plot of decomposition of DMAC in the presence of lithium t-butoxide in Dimethyl Sulphoxide as solvent at 40°C.

$[DMAC]_o = 0.97$ M

$[Lio_tC_4H_9]_o = 0.10$ M

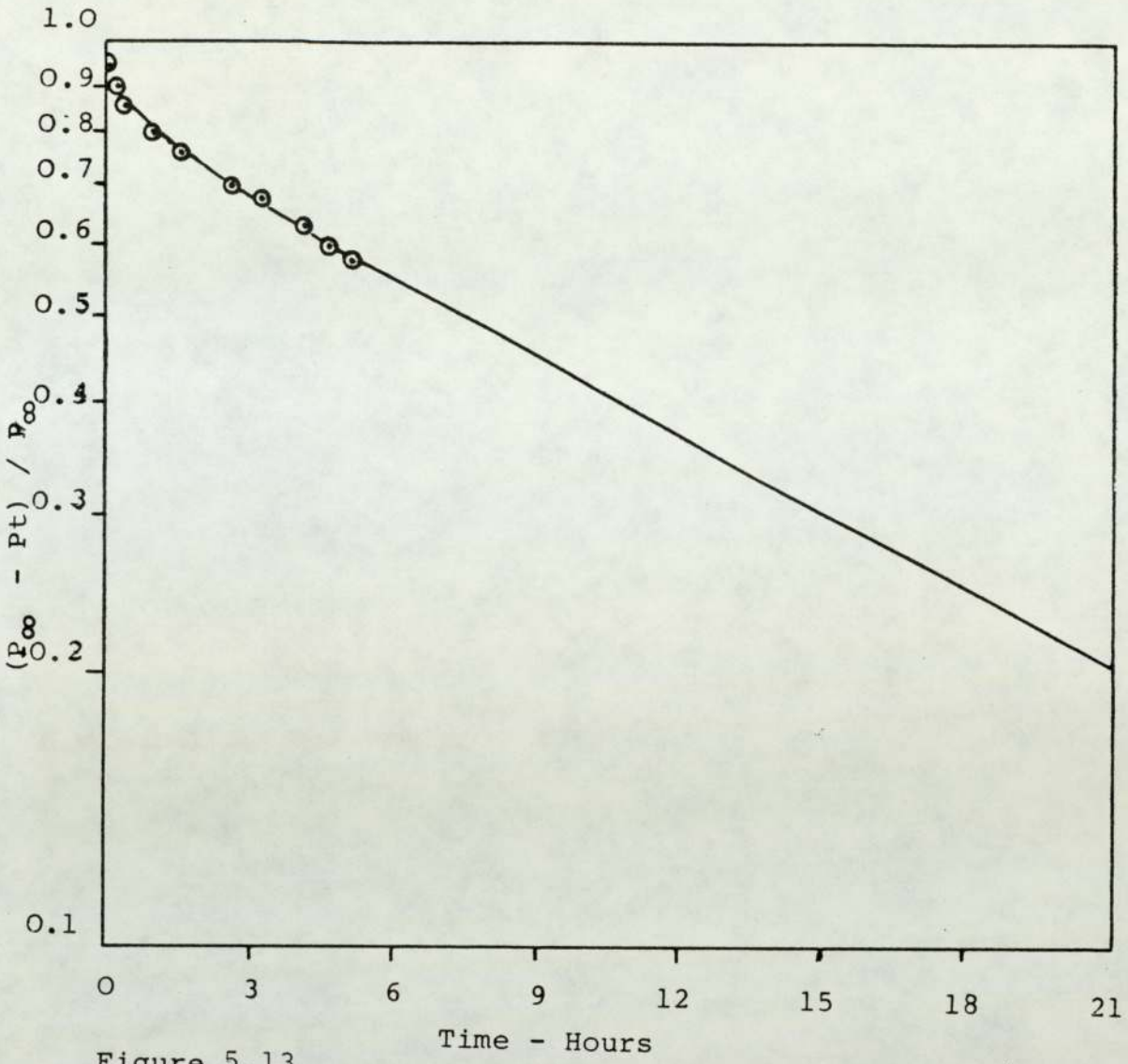


Figure 5.13

First-order rate plot of thermal decomposition of DMAC in Dimethyl Sulphoxide at 48°C.

$[DMAC]_o$ = 1.0 M

5.5 Nature of the Products and Molecular Weight Studies

In this section a study of the products from decomposition of different cyclic monomers (GAAC,GAAS and DMAC) with lithium tertiary butoxide is presented. The products from GAAC and GAAS were obtained after gas evolution (kinetic analysis) experiments using the high temperature apparatus (Figure 2.4). After the experiment had been completed, the solvent was removed under vacuum and the remaining solid subjected to vacuum to remove the traces of solvents. The white solid was washed with ether and finally dried in the vacuum oven at 40°C. Figure (5.14) shows the relative magnitudes of the two carbonyl absorptions of the products in the presence of various quantities of alkoxide and varying co-solvent proportion, the peak at 1740 cm^{-1} corresponding to the carbonyl stretching frequency in the polymer. In addition a peak at 1620 cm^{-1} is shown in the decomposition of GAAC, GAAS and DMAC with lithium tertiary butoxide. The intensity of this peak appeared to be related to the quantity of alkoxide catalyst. In the infra-red spectrum of the decomposition products, the hydroxyl absorption (3500-3400 cm^{-1}) is not clearly defined, that means this polymer differs from that produced by thermal decomposition and pyridine initiation decomposition since their i.r. spectrum shows an absorption at 3400 cm^{-1} due to the presence of hydroxyl groups on the chain ends. The peak at 1620 cm^{-1} suggests a close association of a positively charged species with a carboxylate anion, indicating the possibility of interaction between the monomer and the alkoxide to produce lithium metal carboxylate species (XVII).

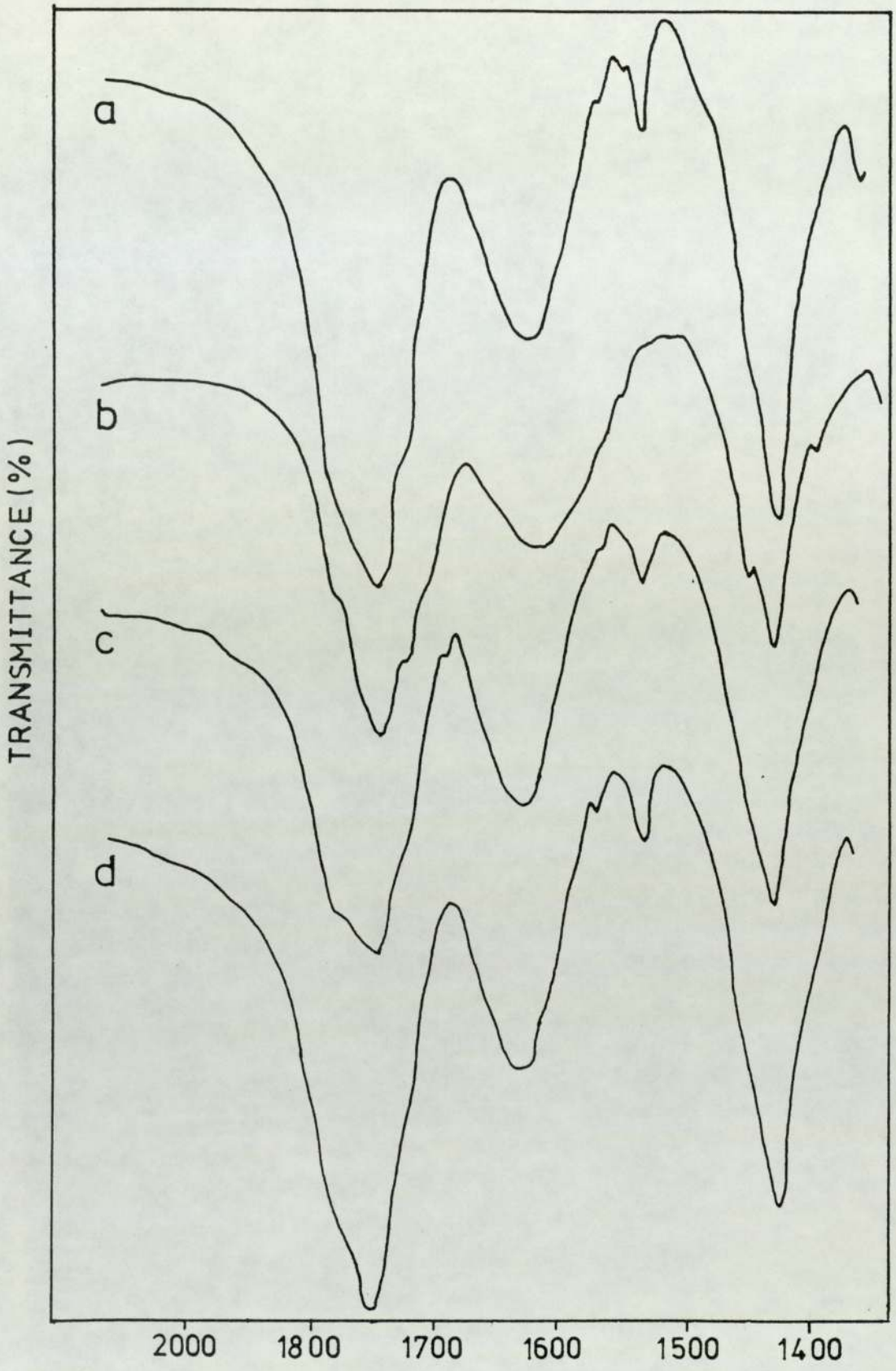


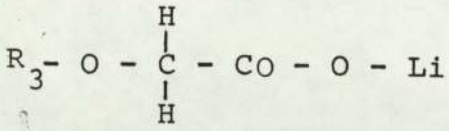
Figure 5.14 Infra-red carbonyl frequencies (ν_{CO}) of products obtained by the decomposition of GAAS, GAAC at 40°C with lithium t - butoxide.

(a) $[GAAC]_o$ = 0.863M, $[Lio_tC_4H_9]_o$ =0.07M in Nitrobenzene:Dekalin = 2:1

(b) $[GAAS]_o$ =0.60M, $[Lio_tC_4H_9]_o$ = 0.109M in Nitrobenzene:Dekalin=1.5:1.5

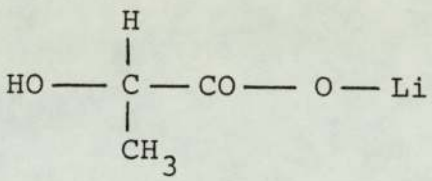
(c) $[GAAS]_o$ = 0.79M, $[Lio_tC_4H_9]_o$ =0.0729M in Nitrobenzene:Dekalin =2:1

(d) $[GAAS]_o$ = 0.60M, $[Lio_tC_4H_9]_o$ =0.053 in Nitrobenzene:Dekalin =1.5:1.5



(XVII)

This idea is supported by an infra - red spectrum of the lithium salt of an α - hydroxy acid (eg. lithium salt of lactic acid XVIII), which has an identical i.r. carbonyl absorption frequency to the product from GAAC and GAAS with catalyst



(XVIII)

A sample of the product of polymer was prepared for determination of molecular weight and molecular weight distribution. This was carried out by decomposition of DMAC with lithium tertiary butoxide in decalin at 35°C for 3 days. When the reaction was complete, the decalin was removed under vacuum and the polymer sample redissolved in THF for G.P.C. analysis. The results of this analysis are presented in Table (5.2). Figure (5.15) shows the infra - red spectrum of the product.

Figure 5.15

Infra-red spectrum of product (polymer) obtained from the decomposition of DMAC at 40°C, solvent Decalin. KBr disc, reference air.

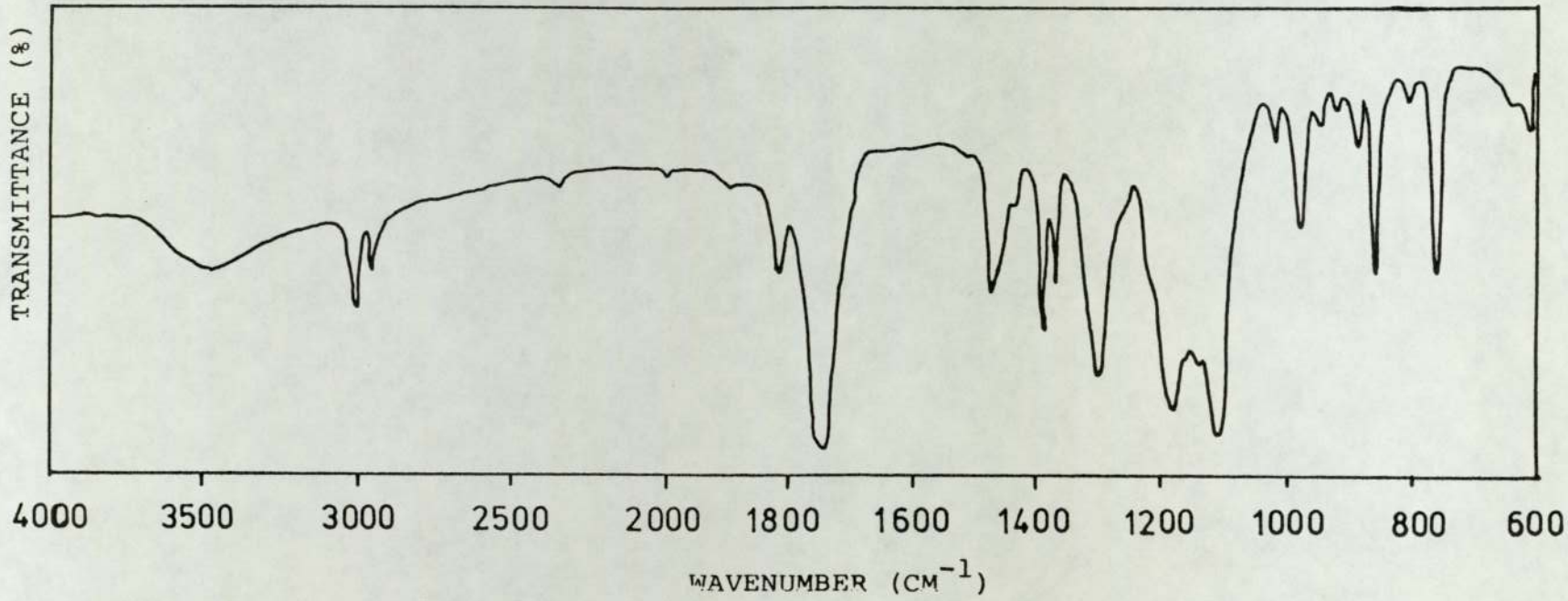
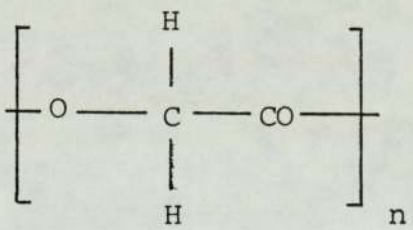


Table 5.2

G.P.C. results of poly - α - ester from lithium t - butoxide initiated polymerisation of DMAC (Solvent Decalin).

$\bar{M}n$	2352	
$\bar{M}w$	21120	$\frac{\bar{M}w}{\bar{M}n} = 8.98$

The polymers (Poly - α - ester) which were produced from decomposition of GAAS and GAAC with lithium tertiary butoxide are consistent with Poly (glycollic acid) and represented by:



(XIX)

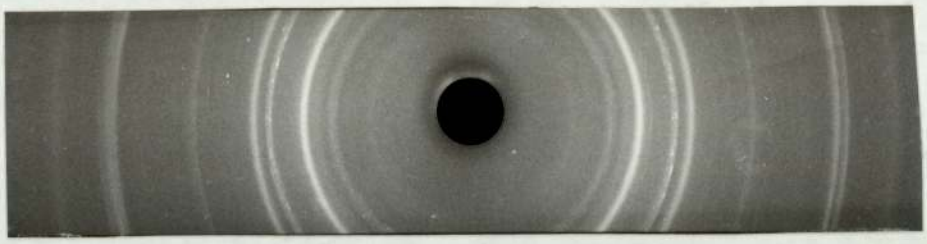
where the value of (n) is governed by the purity of the monomer, solvent and the catalyst. The products are relatively insoluble materials in a wide range of organic solvents (including chloroform and tetrahydrofuran) compared with the unsymmetrical substituted poly - α - esters. For this reason, the difficult solubility of poly GAAC and poly GAAS, particularly in those solvents which are used for G.P.C. study, determination of molecular weight by this technique

gives great difficulty. X-ray studies (Figure 5.16) show that the polymers are crystalline in that there are sharp lines obtained. The crystallinity of poly glycollic acid (XlX) is due to the chains which are packed extremely well thus the interchain distance is at a minimum, an observation substantiated by their insolubility in a wide range of organic solvents. In contrast to poly glycollic acid, poly DMAC (Xll) is rather more soluble in some organic solvents eg.THF. Poly - α - hydroxy isobutyric acid (Xll) which is produced from the decomposition of DMAC with lithium tertiary butoxide is crystalline as shown in the X-ray photograph (Figure 5.16). The diffraction patterns were very similar to those obtained from decomposition of DMAC with pyridine. It appears therefore from the X-ray photographs of polyglycollic acid and poly DMAC, that the difference in the solubility may be related to the crystallinity of these polymers. This may be due either, firstly to the substituents on the polymer chain [it is known that as the substituent groups introduced to the polymer chain become larger, the interchain distance becomes greater] . Secondly the change in the conformation of the polymer structure, thus polyglycollic acid (XlX) which has a planar zig-zag conformation is different from poly DMAC which has a helix conformation. This is thought to occur to accommodate the two methyl groups.

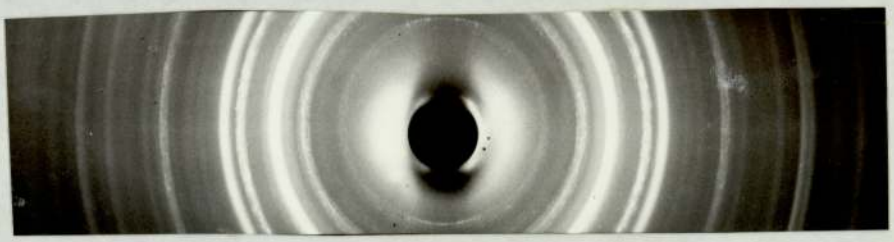
5.6 Discussion

The aim of lithium tertiary butoxide in the present work is as follows:-

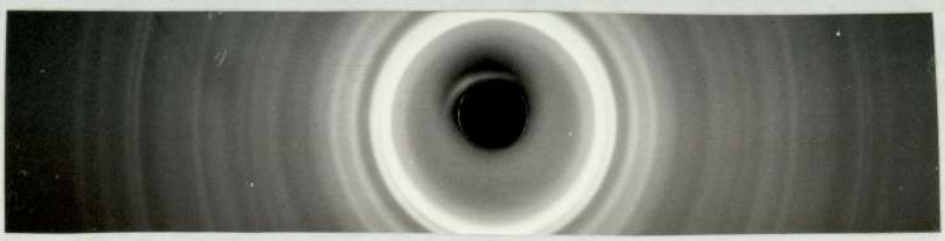
FIGURE 5.16



POLY GAAC



POLY GAAS



POLY DMAC

(1) To study the effect of lithium tertiary butoxide as a catalyst on the simple unsubstituted anhydrocarboxylate GAAC (IX , $R^1 = R^2 = H$) and to the symmetrical substituted anhydrocarboxylate DMAC (IX , $R^1 = R^2 = CH_3$). Anhydrocarboxylates have not previously been studied except for a single experiment recorded by Kosolsumallamas [87] using PFAAC (IX, $R^1 = CH_3$, $R^2 = C_6F_5$) in which polymer was apparently produced.

(2) To find whether lithium tertiary butoxide is suitable to polymerise GAAS, GAAC and DMAC at a reasonable rate and at moderate temperatures and hence to see whether this catalyst is suitable to produce a copolymer from these and other monomers (Chapter 6) which have potential biodegradable applications. For such applications poly - α - esters with hydrogen substituents (eg. poly glycollic acid) are required.

(3) To compare the present work with Crowe's work (who used lithium tertiary butoxide with substituted anhydrosulphites) and with Penny's [91] work (who used bimetallic alkoxide). The present work enables us to study the following points:-

(a) The structure of the monomer i.e. the effect of substituents, the functional group (ie. C = O, S =O)

(b) The solvent medium and the solubility of the alkoxide.

(4) To see whether the mechanism proposed by Crowe can be applied to the anhydrocarboxylate series and to the simple unsubstituted anhydrosulphite (GAAS).

The monomers chosen in this chapter (GAAC, DMAC and GAAS) were therefore selected for the following reasons :

GAAS and GAAC are the simplest anhydrosulphite and anhydrocarboxylate monomers and provide a good basis for kinetic

comparison and enable previous studies by Crowe to be completed. More importantly polyglycollic acid is a useful biodegradable polymer and it would be valuable to modify its structure by copolymerisation . This could be done in two ways. Firstly copolymerisation with the functional monomers discussed in chapter 6 would enable biodegradable drug carriers to be prepared. Secondly copolymerisation with DMAC would introduce symmetrically disposed methyl groups into the chain and thereby enable the rate of biodegradation to be reduced. In the extreme case copolymerisation of DMAC with functional monomers would enable non biodegradable drug carriers to be synthesised.

It is clear from the results presented in this chapter that GAAC, DMAC and GAAS are susceptible to decomposition by lithium tertiary butoxide and one product of this decomposition is polymer (ie. poly - α - ester). The products from the decomposition of GAAC and GAAS with lithium t- butoxide are insoluble in most organic solvents especially in the solvents which are commonly used in the determination of the molecular weight by Gel Permeation Chromotography (eg. THF, orthodichlorobenzene). Therefore the comparison between these polymers and those obtained from thermal decomposition and pyridine initiation is difficult.

It is evident from the results presented in this chapter that the mechanisms involved in the decomposition of anhydrosulphite (GAAS) and anhydrocarboxylate (GAAC, DMAC) in the presence of alkoxides are basically different from those involved in the thermal polymerisation of these compounds. The most important features of the alkoxide initiated reactions may be summarised as follows:-

(i) The reaction is first - order with respect to both monomer and initiator in the early stages.

(ii) Addition of lithium t - butoxide to monomer gives the product appearing to contain carboxylate anion (1620 cm^{-1}) followed by the slower appearance of polymeric products.

(iii) In the later stages, after 50% conversion, the rate slows down to a level below first order behaviour.

(iv) The lithium predominantly associated with the low - molecular weight product rather than with the polymer.

(v) The rate of decomposition of GAAC is slowed somewhat by the addition of a polar solvent.

(vi) The molecular weight distribution of the poly - α - ester produced from lithium tertiary butoxide with the GAAS, GAAC and DMAC is more complex than that of thermally prepared and pyridine initiated polymer. The molecular weight distribution is broader than obtained by other polymerisation methods.

Analysis of the decomposition products from GAAS and GAAC with lithium tertiary butoxide shows that there are two products. The first is the polymeric product ($\gamma_{C=O}$ = 1740 cm^{-1}) and the second is non - polymeric product ($\gamma_{C=O}$ = 1620 cm^{-1}). Hence the kinetic behaviour of these reactions can be explained in that the non - linearity plot (Figures 5.2,5.6) is due to the onset of heterogeneity of the system due to appearance of the precipitate (polymer) during the reaction. However, all the reaction profiles showed first - order behaviour but because the heterogeneity makes the understanding of the reaction order difficult. This will be discussed in more detail in this section.

Lithium tertiary butoxide has been employed as catalyst in polymerisation of MEAS (methyl ethyl anhydrosulphite) and other anhydrosulphites at different conditions in decalin as solvent.[93] The kinetics of polymerisation were found to be first order with respect to both monomer and lithium t - butoxide. The catalyst was not completely consumed during the reaction and the molecular weight of the product, poly - α - ester, was little changed by change in both monomer and initiator concentration (maintaining constant $[M]_o / [I]_o$).

It is apparent from these results that there are many similarities between the lithium tertiary butoxide induced decomposition of some anhydrosulphites (Crowe's work) and the present work, especially with regard to the i.r spectra of the products and the kinetic behaviour of these compounds. Table (5.3) shows the product and the first order rate constant for the decomposition of anhydrosulphites and anhydrocarboxylates which are decomposed by lithium tertiary butoxide. However, since the solubilities of the monomers which have been used by Crowe are different from the monomers which are used in the present work, therefore comparison between these monomers is difficult.

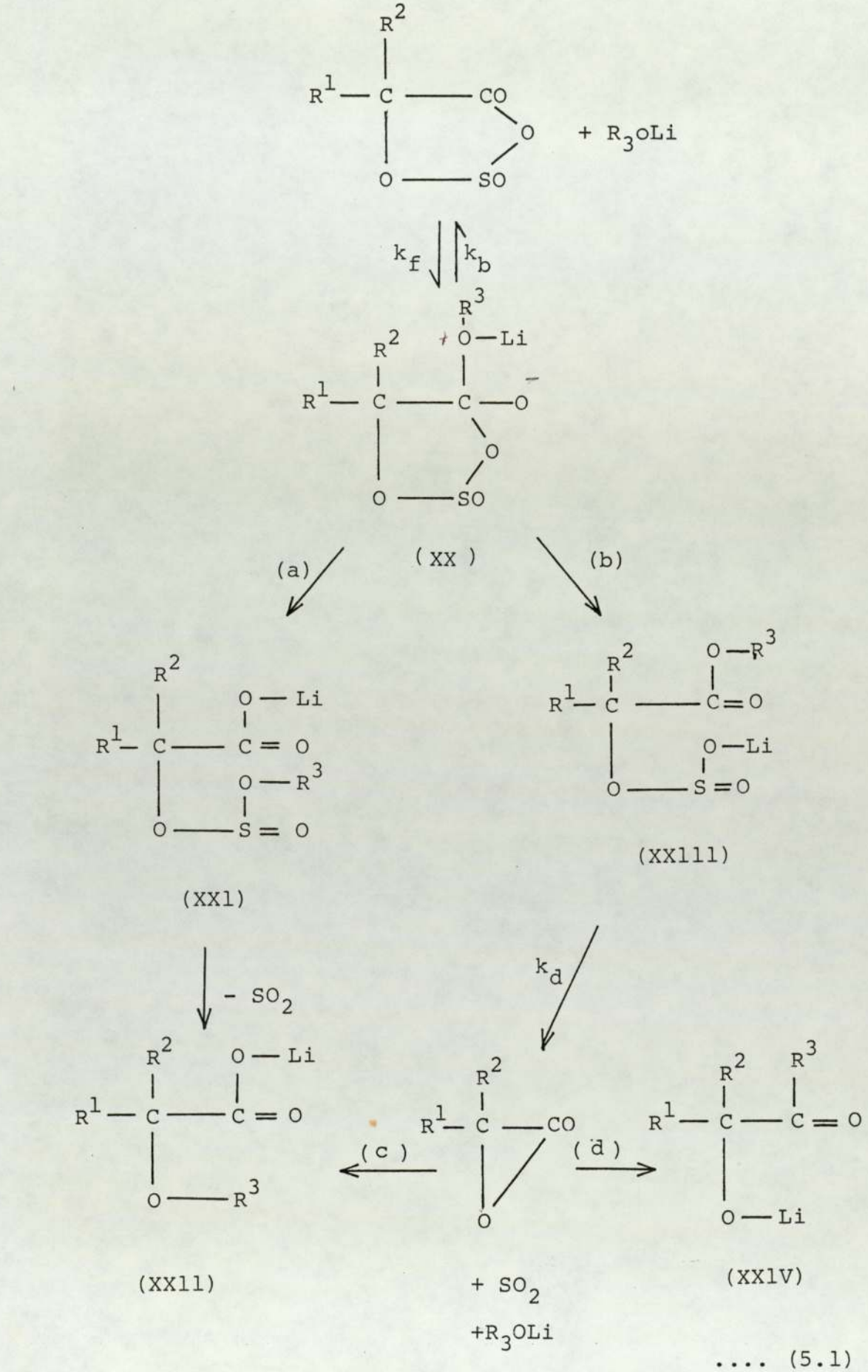
Since the present study and the work by Crowe show similarity in various respects, it can be assumed that the same or a very similar reaction mechanism governs the chemical behaviour of anhydrosulphites and anhydrocarboxylates, especially in relation to lithium tertiary butoxide.

Crowe[93] derived a reaction mechanism, according to the characteristic features of alkoxide reactions, which he called the 'Modified Reactive Intermediate' mechanism to explain the results he obtained. In relation to this work, the

Table (5.3) Decomposition of anhydrosulphites and anhydrocarboxylates of ∝ - hydroxy carboxylic acid by lithium tertiary butoxide.

Monomer	Solvent	$[M]_o$	$[I]_o$	Temp. ^oC	Product	Rate constant
MEAS	Decalin	0.75	0.0082	40	Polymer	58.0×10^{-4} mol.$^{-1}$ l.sec^{-1}
MEAS	THF			18	Polymer	-
c` pent. AS	Decalin	0.75	0.0082	40	Polymer	338×10^{-4} mol.$^{-1}$ l.sec.$^{-1}$
HBAS	Decalin	0.75	0.0082	40	Polymer	482×10^{-4} mol.$^{-1}$ l.sec.$^{-1}$
DEAS	Decalin	0.75	0.0082	40	Polymer	2.98×10^{-4} mol.$^{-1}$ l.sec.$^{-1}$
DMAC	Decalin	0.526	0.13	25	Polymer	
PFAAC	Toluene -THF	0.30	0.02	45		-
GAAC	Toluene	0.50	0.027	30	Polymer	3.5×10^{-4} sec.$^{-1}$
GAAC	nitrobenzene/ Decalin	0.803	0.07	40	Polymer	5.66×10^{-5} sec.$^{-1}$
GAAS	nitrobenzene/ Decalin	0.79	0.0729	40	Polymer	5.34×10^{-5} sec.$^{-1}$
GAAS	Decalin	2.0	0.025	40	Polymer	

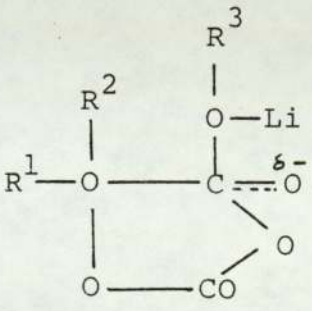
following scheme has been suggested by Crowe.



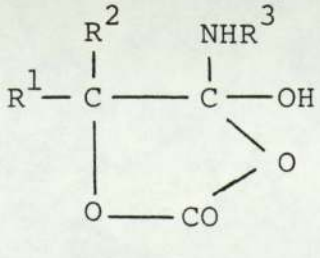
.... (5.1)

This scheme involves rapid attack of lithium tertiary butoxide on the monomer, at the C-4 position of the ring, by the nucleophilic oxygen atom of the alkoxide and formation of a charge transfer complex (XX), which can rearrange in two ways. Route (a) involves the formation of a metal carboxylate (XXl) which decomposes slowly to yield the carboxylate ester (XXll). Route (b) is fast, and may involve a second charge transfer intermediate (XXlll) which breaks down to give a highly reactive intermediate, which is shown as an α - lactone, sulphur dioxide is released and the alkoxide regenerated. This is followed by a rapid reaction of the α - lactone with any nucleophile(ie. the growing polymer chain) which may be present. The lithium-t-butoxide is able to react with the α - lactone in either of two ways, (c) to give an active carboxylate ester (XXll) by attack the alkoxide at the substituted carbon of the α -lactone, and (d) by attack at the carbonyl of the α - lactone to regenerate a derived alkoxide (XXlV).

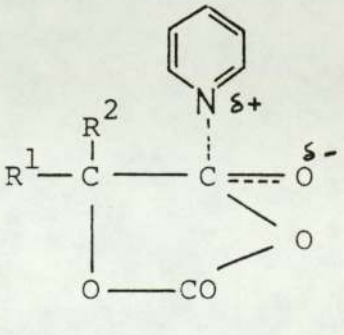
The nature of the intermediate (XXV) produced in the lithium tertiary butoxide reaction will be quite different from transition states produced from the reaction of nucleophiles possessing transferable protons for example with primary amines (XV). Also even it is different from that produced from pyridine initiation (XlV).



(XXV)

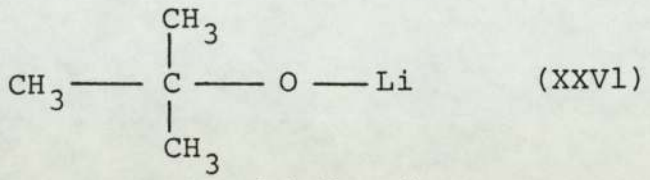


(XV)



(XlV)

The difference between these structures is due to the nucleophilicity of oxygen of the lithium tertiary butoxide molecule, which attacks the C (4) carbonyl (being less than the lone pair of the nitrogen of pyridine) and also because the oxygen in the alkoxide molecule (XXVl) which attacks C(4)



(XXVl)

carbonyl is more sterically hindered.

Comparison must be made between the products in the present work produced from lithium tertiary butoxide decomposition of GAAS, GAAC and DMAC according to the Equation (5.1). Firstly the products are different from those produced thermally and from pyridine initiated decomposition principally as a result of the non polymeric products. GAAS and GAAC give products with the same i.r. spectrum (Figure 5.14) in that the polymeric product ($\nu_{c=o}$ = 1740 cm^{-1}) and non-polymeric product ($\nu_{c=o}$ =1620 cm^{-1}) are of similar quantity while in the case of the products from DMAC (Figure 5.15), the quantity of the non-polymeric product is less. This may be due to effect of electronic structure of the ring and consequently the reactivity of C (4) carbonyl group. Thus the polymer producing reaction route (d) (Equation 5.1) is the predominant reaction with DMAC and the minor product is the carboxylate salt.

It may be that in the case of DMAC the route to polymer will involve a loose charge transfer complex rather than the formal transition state depicted in Equation (5.1). In this case the polymerisation would proceed in an analogous way to that with pyridine as shown in Equation (3.5) Chapter 3.

The kinetic scheme in this case could be written as shown below.

The intermediate $(MO\overset{R}{\underset{Li}{<}}{}^{*})$ (M - cat) would be involved as follows.

$$\text{Monomer + catalyst} \underset{k_b}{\overset{k_f}{\rightleftharpoons}} \left[\text{M - cat}\right] \xrightarrow{k_d} \text{product + } CO_2 \text{ + cat} \quad \ldots\ldots(5.2)$$

The rate constants k_f, k_b and k_d describe the forward and reverse reactions in the formation and decomposition of charge transfer complex to form α- lactone (product) respectively. As the reactivity of α- lactone is very high its rate of reaction is not considered. The equilibrium constant K is given by $K = \frac{k_f}{k_b}$ ..... (5.3)

The rate of formation of product is given by

$$\frac{d[\text{Prod}]}{dt} = k_d \left[\text{M - cat}^{*}\right] \quad \ldots\ldots \quad (5.4)$$

the concentration of the intermediate $\left[\text{M - cat}^{*}\right]$ and reactants are related through the equilibrium constant.

$$\left[\text{M - cat}^{*}\right] = K \left[\text{M}\right]\left[\text{Cat}\right] \quad \ldots\ldots(5.5)$$

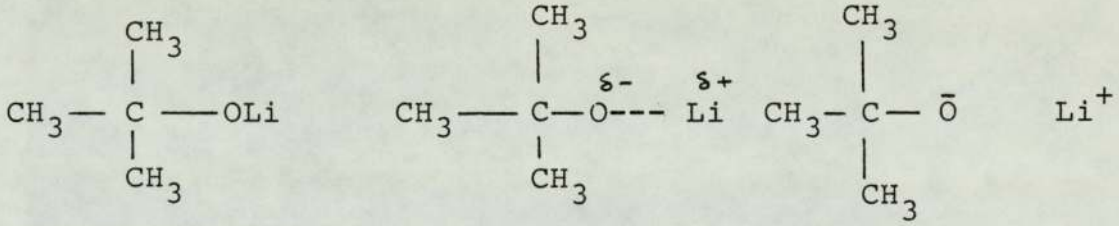
combining equation (5.4) and (5.5).

$$\frac{d[\text{Prod}]}{dt} = k_d K \left[\text{M}\right]\left[\text{Cat}\right] \quad \ldots\ldots (5.6)$$

The concentration of $\left[\text{M - cat}^{*}\right]$ is expected to be small and is not expected to change significantly through the reaction. As the reaction between the catalyst with monomer is fast so k_f and k_d are likely to be large compared to k_b.

The solvent is one of the most important factors which influence the rate of a chemical reaction. There are basically two properties of solvents which can affect the rate of a

reaction. Firstly, the polarity of the solvent as measured by its dielectric constant (ϵ), is important when the reaction proceeds through an activated intermediate complex (present work) where solvation affects the stability of that intermediate, or where charge separation occurs. Secondly, the donicity (ability of the solvent to donate an electron pair to a suitable electron acceptor) is also important in determining the rate of a particular reaction particularly in reaction involving nucleophiles. Considering the organometallic compounds , for example lithium tertiary butoxide in solution which can exist in a variety of forms as shown below:



(XXV1) (XXV11) (XV111)

Structures (XXV11) and (XXV111), which have an ionic character are more probable in polar solvent, by association with solvent molecules which stabilise their separation into the ions. The evidence for the existence for structure (XXV11) comes from vapour pressure osmometry study[93] using polar solvent (THF) in which a dimer form was detected, perhaps explained by association of two or more ion pairs of solvated lithium tertiary butoxide molecules. In the presence of a co-solvent mixture (present work) such as nitrobenzene (polar solvent), the catalyst and the monomer could be solvated by the polar component of the co-solvent. This would impose difficulties in the approach of monomer and active catalyst and hence a

reduction in rate is observed (comparison Figure 5.2 and 5.5). The departure from first order behaviour during the latter stages may be due to a diffusion - controlled situation in which the monomer has to penetrate the solvent cloud surrounding the chain end of the polymer. This assumes that most of the alkoxide initiator disappears in the earlier first order portion of the reaction. The onset of heterogeneity is bound up with this problem and makes exact interpretation of the kinetic profiles very difficult.

The difficulty of the solubility of DMAC in decalin presents a considerable problem for kinetic study with lithium tertiary butoxide. Dimethyl sulphoxide (DMSO) was examined as a solvent due to the solubility of both monomer and the catalyst. DMSO is a dipolar aprotic solvent, is a strong electron donor, and has a high polarity, therefore, alkoxides with DMSO are among the most strongly basic systems. The explanation of the non-lineanty of the plot, in the case of DMSO as a solvent may involve the following explanations:-

(1) Reaction of carbon dioxide (produced from the reaction) with the solvent.

(2) The interference of the solvent with the attack of catalyst at the C(4) carbonyl of the monomer to cause a decrease in the rate of reaction.

(3) Dimethyl sulphoxide reacts in some way with the catalyst.

(4) Reaction of the evolved carbon dioxide with the catalyst in the presence of this solvent.

More work would be necessary to resolve these points.

In this chapter, it is possible to observe the comparison between anhydrosulphites and anhydrocarboxylates in terms of their reactivity towards lithium tertiary butoxide. From the results which are presented in this chapter, it appears that glycollic acid anhydrocarboxylate (GAAC) is more succeptible to decomposition than glycollic acid anhydrosulphite (GAAS). This may be due to the following reasons:-

(1) The solubility of sulphur dioxide gas (evolved from GAAS) is greater in the solvent which was used in the kinetic study, than carbon dioxide gas (evolved from GAAC).

(2) Sulphur dioxide is more acidic than carbon dioxide, hence it may be lower than the basicity of alkoxide.

In the light of this difference in reactivity it is rather suprising that when sodium methoxide in nitrobenzene was used as a catalyst with dimethyl anhydrocarboxylate (DMAC), section 5.4, no effect on the rate of decomposition was observed. This may be due to the fact that the substituents (methyl groups) in the monomer are comparatively non - polar and therefore their influence on reactivity is predominantly steric. Table (5.4) shows the effect of sodium methoxide on different cyclic monomers with different solvents.

The main problem with sodium methoxide is its low solubility in organic solvents which brings even greater problems of heterogeneity than with lithium tertiary butoxide.

Table (5.4)

Effect of Sodium methoxide on different cyclic Monomers

Monomer	Solvent (Temp ^{o}C)	Nature of the product	Ref
DMAC	Dioxan (25)	No - polymer	60
DMAC	Benzene	No - polymer	60
DMAC	Nitrobenzene (40)	No - polymer	
HBAS	Benzene	No - polymer	
Cl - HBAS	Benzene (30)	Polymer	87
DEAS	Nitrobenzene (25)	Polymer	93

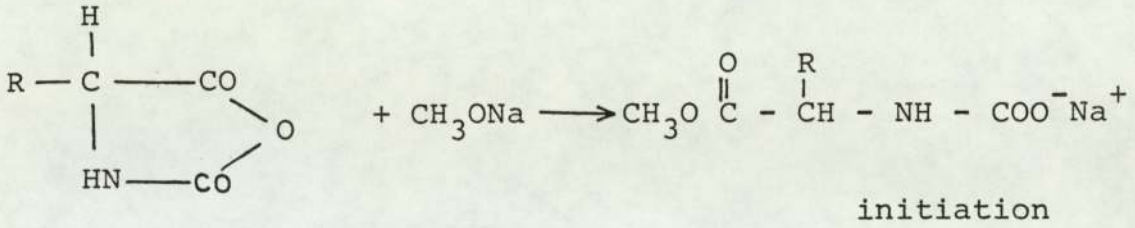
For the sake of comparison, it is appropriate to outline the effect of alkoxides in carboxyanhydrides of α - amino acids (NCAs). Sodium methoxide was used as an initiator in the preparation of high molecular weight polymers from NCAs in solvents such as dioxan, benzene and THF. The main features of this reaction are :-

(1) slow induction periods up to about 30% conversion, then the reaction progresses by means of a first-order reaction;

(2) the first-order rate constant is about 100 times faster than that found in the primary amine - initiated reaction;

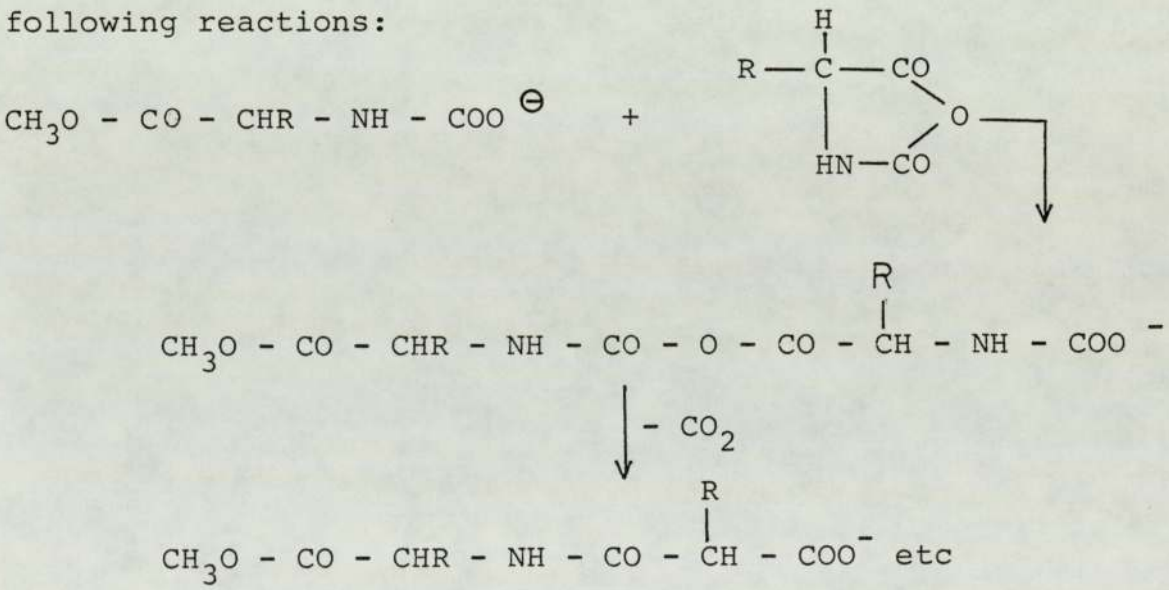
(3) very high molecular weight, up to $\bar{M}w$ 10^6 were obtained.

The mechansim of action of alkoxides on N.C.A.S. has been well studied [51]. According to this mechanism, a strong base initiator such as sodium methoxide reacts with the monomer via nucleophile attack at the 5 - carbonyl of the N - carboxy - anhydride ring:

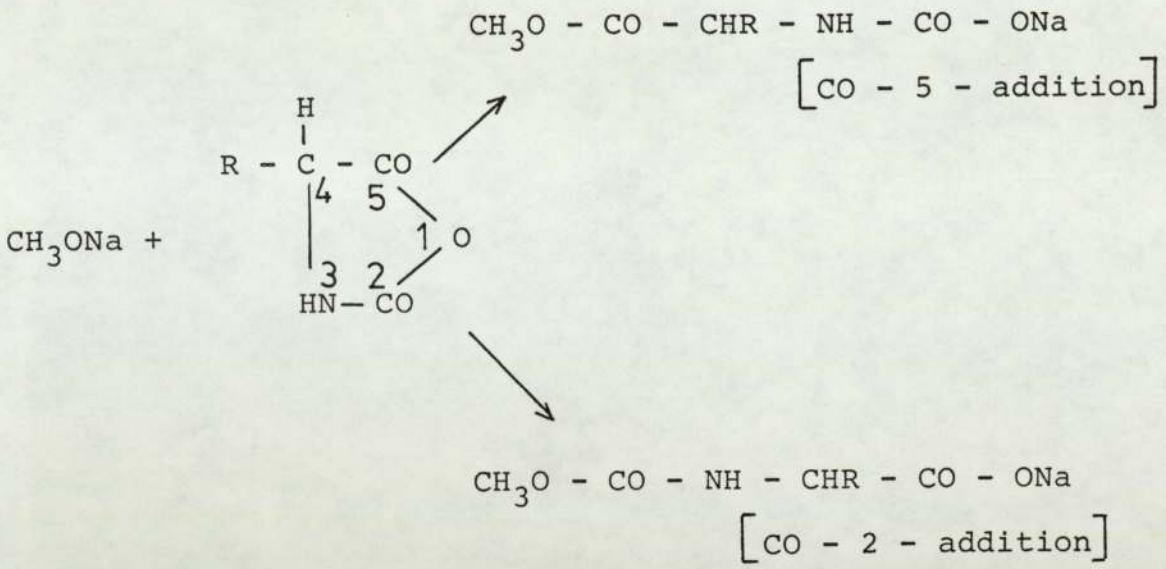


initiation

The nucleophilic attack of the base results in opening of the ring and formation of a carbamate species which is responsible for chain propagation. The chain grows by addition of carbamate to the new N - carboxyanhydride molecule, with formation of the intermediate carbamate - carboxyl mixed anhydride, followed by carbon dioxide evolution and generation of a new reactive carbamate ion, according to the following reactions:



This reaction mechanism was originally proposed on the basis of the fact that at equimolar concentrations the reaction of N - carboxyanhydrides with sodium methoxides leads to the formation of two products: the sodium salt of the carbamate ester and the sodium salt of the N - carboxy amino acid ester.



According to the above mechansim, each polymer chain must contain a fragment of the initiator.

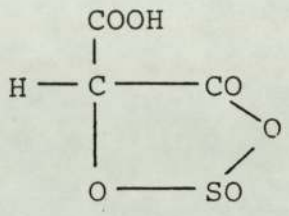
Although there are certain apparent similarities in actual product of the reaction of NCAs and anhydro-carboxylate of α - hydroxy acid with alkoxide the kinetic behaviour and subsequent path way of the reaction appears to be quite different.

As in the case of pyridine reaction, the effect of nitrogen on the chemistry of NCA ring makes similarities with the analogous hydroxy acid derivatives relatively few.

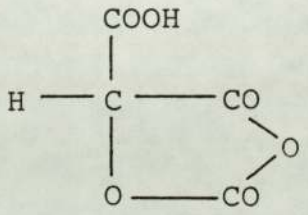
CHAPTER 6

MONOMERS CONTAINING FUNCTIONAL GROUPS

This chapter is particularly concerned with the synthesis of cyclic monomers of ∝- hydroxy carboxylic acids (1V) with functional substituents (eg. a COOH group), namely Tartronic acid anhydrosulphite (XX1X) and Tartronic acid anhydrocarboxylate (XXX).



(TAAS)
(XX1X)



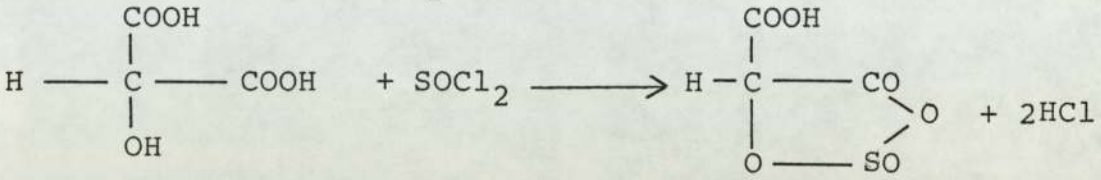
(TAAC)
(XXX)

Synthetic polymers with functional groups especially where the functional group is a biologically active group are currently receiving considerable attention. Since, such polymeric drugs as those with biodegradable functional groups, represent novel drug delivery systems, in addition to the above mentioned monomer synthesis, preparation of poly - ∝- esters with potential biologically active groups ie. containing suitable biodegradable binding site for drugs were examined.

The simpler members of the poly - ∝- ester series are known to be biodegradable (eg. polyglycollic acid, X, $R^1 = R^2 = H$ and polylactic acid, X, R^1=H, $R^2 = CH_3$). The type of ring opening reaction described in this thesis possesses suitable synthetic versatility to give polymers with suitable binding sites. In contrast the simple self polyesterification of the parent acids would be unable to do this.

6.1 Synthesis of Tartronic Acid Anhydrosulphite

Tartronic acid anhydrosulphite (XXIX) was prepared from the reaction of tartronic acid [(XXXI) purified by standing over phosphorous pentoxide in a vacuum desiccator to remove the moisture] and thionyl chloride, Equation 6.1



(XXXI) ... 6.1

0.1 moles of the tartronic acid was slurried in 50 mls. anhydrous ether and 0.15 moles of thionyl chloride was added dropwise over a period of two hours maintaining the temperature below $0^{o}C$. On completion of the addition of thionyl chloride, the mixture was allowed to warm up to room temperature and the reaction continued for four days. During this time the insoluble acid disappeared and the solution turned to a pale yellow colour. The excess thionyl chloride and ether were stripped off under vacuum to leave a pale yellow viscous liquid.

The most important impurity from the above type of reaction is known to be α - chloro acid chloride. The removal of this species is essential for controlling polymerisation of TAAS, and is best achieved by chemical rather than physical methods. Although the presence of chloride containing impurities in anhydrosulphite synthesis is minimised by using thionyl chloride with the copper salt of the α - hydroxy acid, this technique is not applicable in the case of tartronic acid. This is due to the presence of the two carboxylic acid groups in the parent acid (XXXI)

which are equivalent . In other words it is impossible to bond only one of these carboxylic groups to a metal ion without first protecting the other. The high boiling point of TAAS coupled with its low thermal stability in fact precluded the use of vacuum distillation, as mean of purification since the required distillation temperature leads to the complete decomposition of TAAS. Treatment with silver oxide (as described in chapter 2) has proved to be most successful in the removal of chlorine containing impurities due to the minimal decomposition occuring during purification by this method. The purified monomer was stored below $0^{o}C$ in order to inhibit the decomposition of this material. The formation of chloride ion impurities during the action of thionyl chloride on tartronic acid, may be illustrated by outlining the reaction scheme shown in Equation (2.9).

Although the second carboxyl function in difunctional α - hydroxy acids such as tartronic acid (XXXI) may be expected to interfere in the synthesis of anhydrosulphites via reaction of side chain functional groups, this does not present a problem in TAAS synthesis.

To prevent this interference the second functional group is usually protected by a reversible blocking reagent. The removal of the blocking reagent from the formed monomer or the polymer requires the need to use reagents which may cause decomposition of the monomer. Equation(6.4) illustrates that since the hydroxyl group is more reactive to thionyl chloride than the carboxyl the need for this is overcome in tartronic acid.

Characterisation

The product from the above mentioned reaction was

initially and most conveniently characterised by infra-red spectroscopy. Because the carbonyl absorptions for carboxylic acid, carboxylate anion, acid chloride, poly - α - ester and anhydrosulphite are quite distinct and characteristic, this technique provides an excellent indication of the nature of the product. The spectrum obtained is shown in Figure (6.1) The peak at 1750 cm^{-1} was attributed to the carboxylic acid group substituent on the ring since its position was similar to that of the carbonyl absorption shown in the infra-red spectrum of tartronic acid (Figure 6.2). The peak at 1820 cm^{-1} was attributed to the carbonyl group in the anhydrosulphite ring. The high carbonyl absorption frequency is characteristic of that in the strained anhydrosulphite ring. The frequency of this carbonyl absorption is higher than that of both the parent acid and the decomposition product of the ring. There is a peak at 1230 cm^{-1}, which was assigned to the SO group in the anhydrosulphite ring. Elemental analysis of anhydrosulphites is of little use due to the sensitivity of anhydrosulphites to moisture and thermal instability. However, the hydrolysis of the anhydrosulphite to the parent acid coupled with the evidence of gas evolution experiments which enables the quantity of sulphur dioxide liberated to be estimated provides support for the identity of the compound.

The monomer was also characterised by n.m.r. which shows that there is an expected change in the proton of carboxylic acid groups of tartronic acid (XXXl) with that of the carboxylic acid group of the monomer (XXlX).

Figure 6.1

Infra-red spectrum of Tartronic Acid Anhydrosulphite.

The spectrum was recorded as a thin film using KBr plates, the reference cell was air.

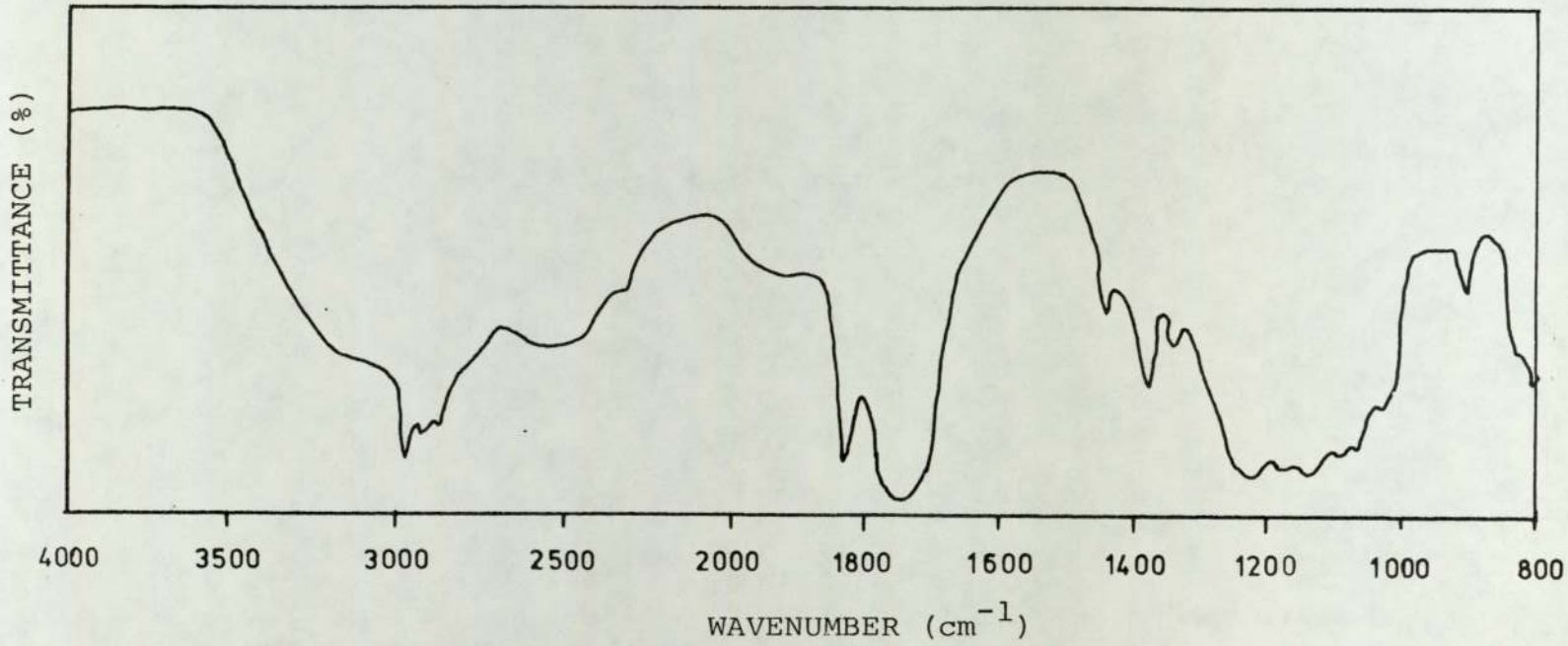
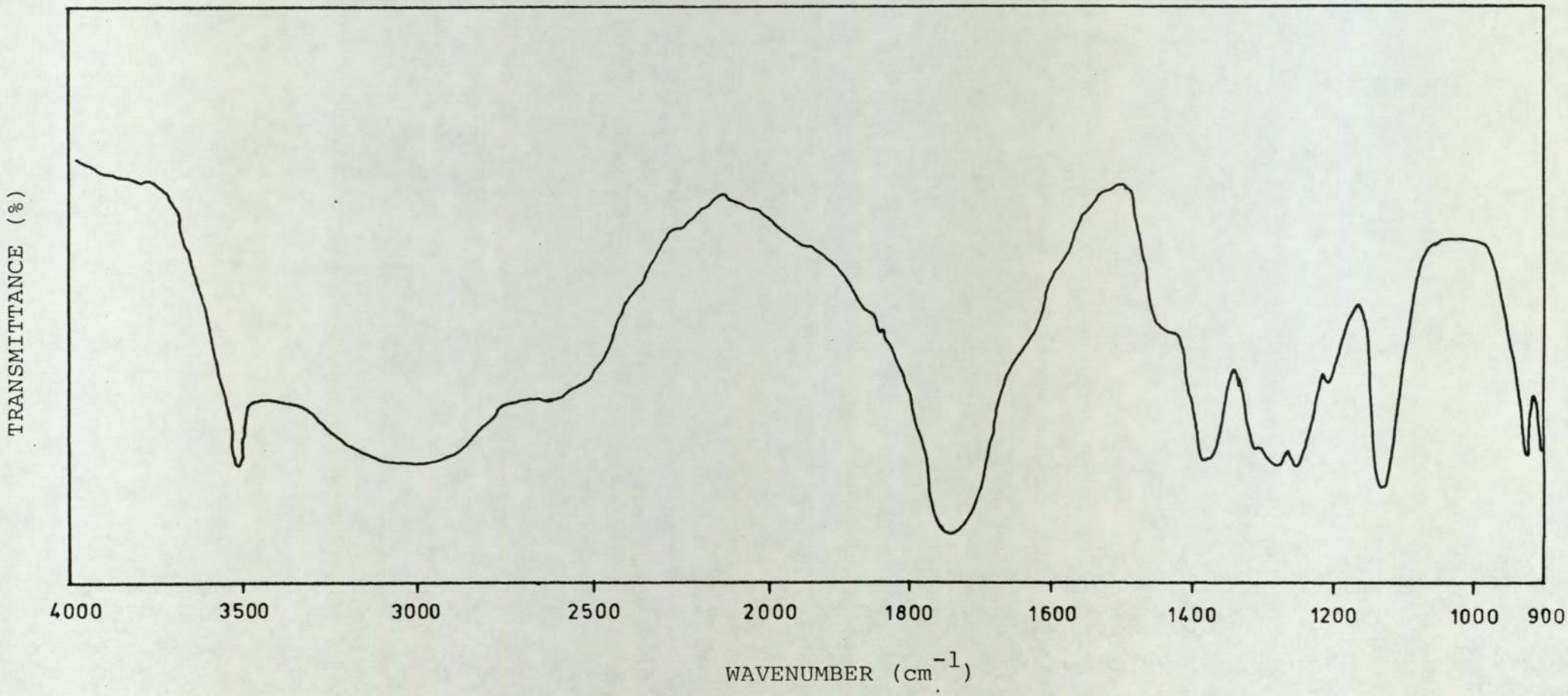


Figure 6.2

Infra-red spectrum of Tartronic Acid. The spectrum was recorded as KBr disc, the reference cell was air.



6.2 Thermal Decomposition of Tartronic Acid Anhydrosulphite (Bulk Polymerisation) - Kinetic Measurement and Results

The thermal decomposition of tartronic acid anhydrosulphite (XXIX) was carried out in bulk at three temperatures, viz. 60, 70, and 80°C, using the gas evolution techniques described in chapter 2 and the apparatus shown in Figure (2.4) . Measurement of pressure rise was carried out with the aid of a cathetometer. Monomer decomposition was shown to be a first order process by plotting the gas evolution data graphically in the form log $(P_\infty - P_t) / P_\infty$ versus time. The primary pressure vs. time plots are converted to the corresponding semilogarithmic plots log $(P_\infty - P_t) / P_\infty$ vs. time shown in Figure (6.3). The overall process can therefore be expressed by the Equation (6.2)

$$\frac{d[P]}{dt} = -\frac{d[M]}{dt} = \frac{d[SO_2]}{dt} = k_1[M] \qquad \ldots\ldots(6.2)$$

Where $[P]$, $[M]$ and $[SO_2]$ refer to the concentrations of polymer, monomer, and sulphur dioxide respectively, and k_1 refers to the first order rate constant. From Figure (6.3), the order, the half life and the rate constant for the thermal decomposition process at a particular temperature can be found, as shown in Table (6.1). From an initial study of these graphs it was deduced that tartronic acid anhydrosulphite decomposed, probably thermally, by a mechanism which is first order with respect to monomer at all three temperatures thus three values for the rate constant for the decomposition of the anhydrosulphite are obtained which are dependent - upon temperature. This enabled the plot of log k_1 against temperature to be made which produces a straight line (Figure 6.4). From the slope

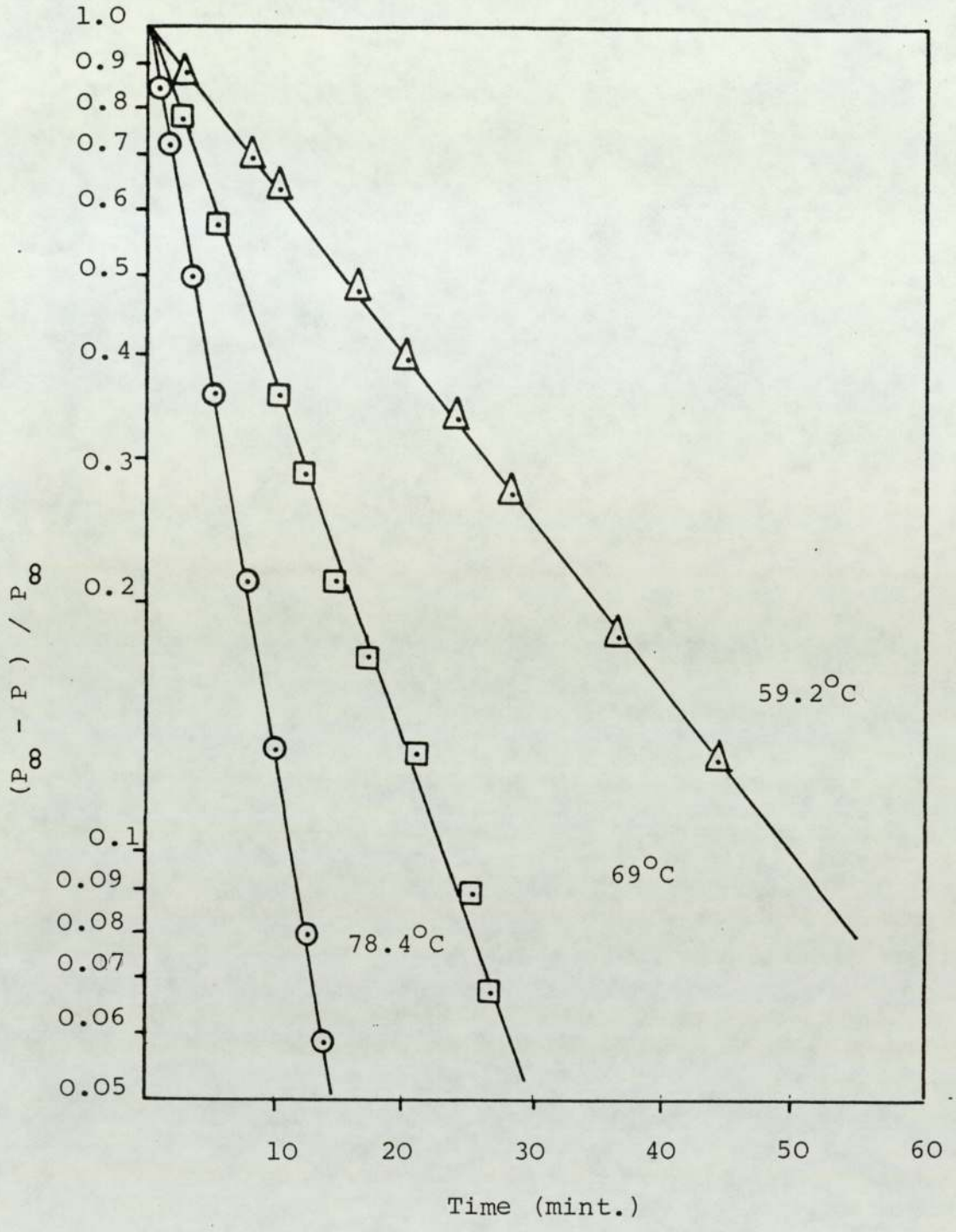


Figure 6.3 First order semi-logarithmic plots for the thermal decomposition (Bulk) of tartronic acid anhydrosulphite.

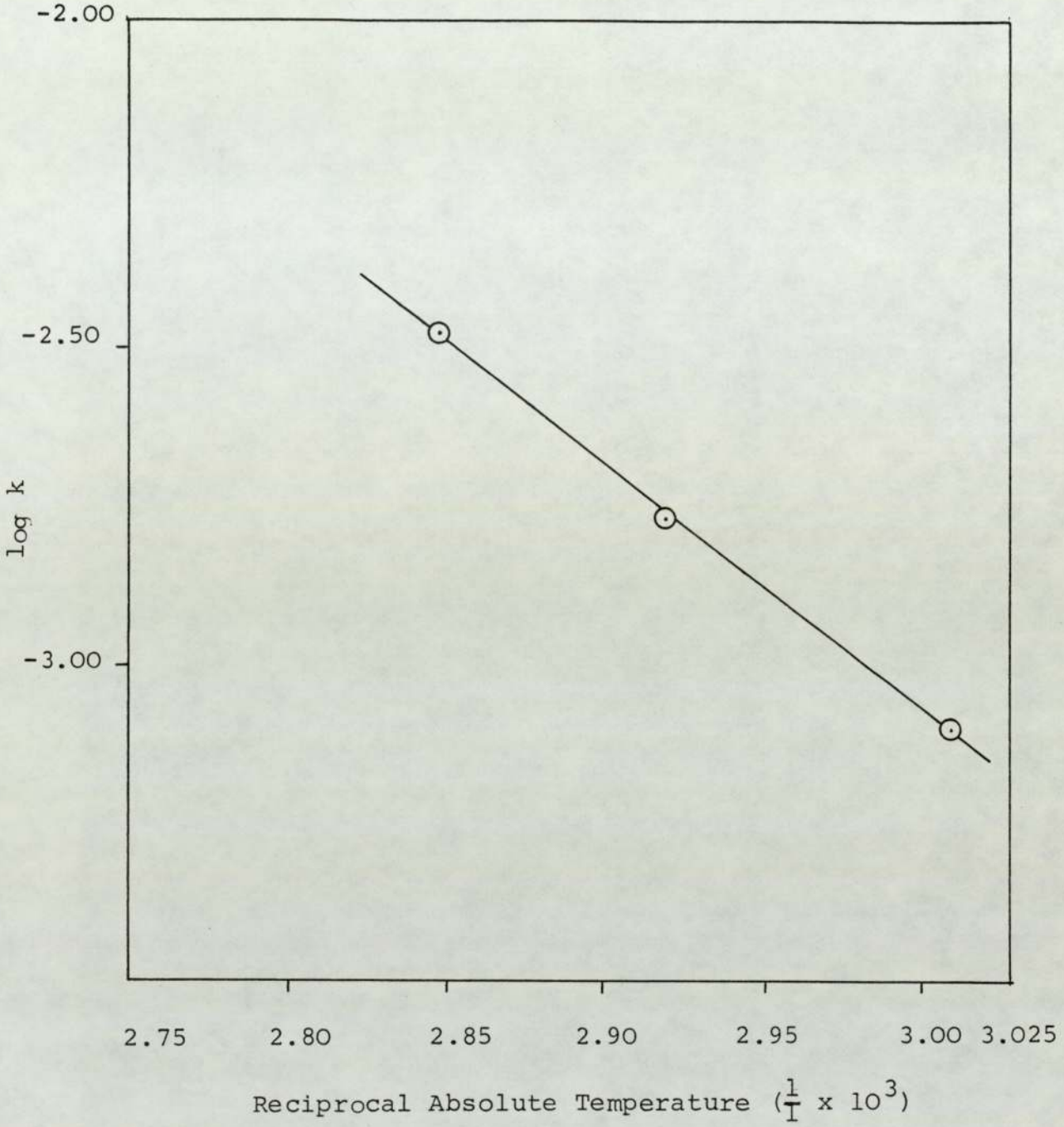


Figure 6.4 Arrhenius plot of the first order rate constant log k_1 versus the reciprocal of the absolute temperature for the thermal decomposition (Bulk) of Tartronic Acid Anhydrosulphite.

of this line the energy of activation for the breakdown of the anhydrosulphite ring is calculated. This together with the other activation parameters derived from the Arrhenius plot are shown in Table (6.1).

Table 6.1

First order rate constant (k_1), half lives ($t_{\frac{1}{2}}$), energy of activation (Ea), entropy of activation ($\Delta S^{\ddagger}$) and frequency factor (A) for the bulk polymerisation of TAAS (tartronic acid anhydrosulphite).

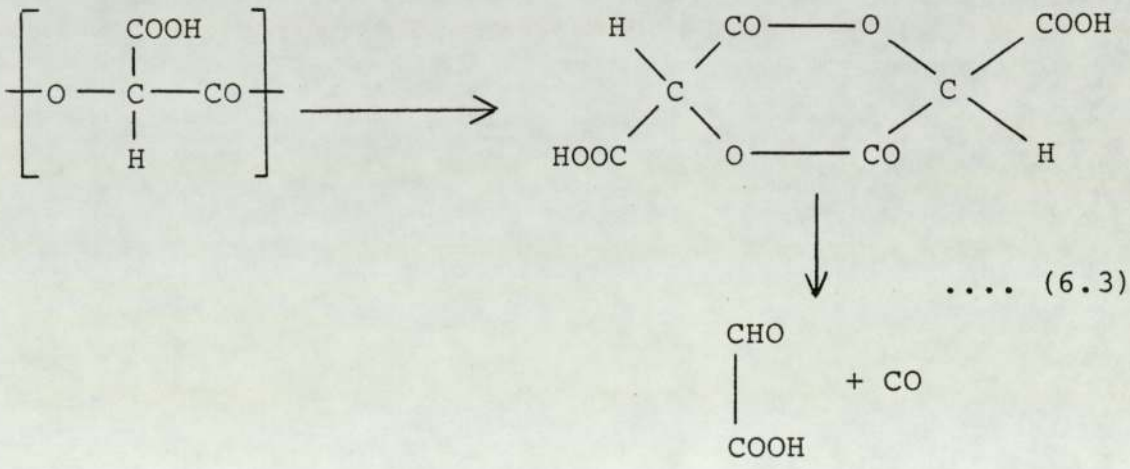
Temp. ^{o}C	$10^3 \frac{1}{T^{o}K}$	t ½ mins.	$10^3 k_1$ ($sec.^{-1}$)
59.2	3.01	15	0.7
69	2.92	7	1.65
78.4	2.85	3.5	3.3
E (K.J. $mol.^{-1}$)		18.00	
A ($sec.^{-1}$)		1.9×10^{10}	
$\Delta S^{\ddagger}$ ($J.K^{-1}mol^{-1}$)		- 48.9	

6.3 Reaction Products

The product from thermal decomposition of TAAS was characterised by infrared spectroscopy. The spectrum shows a peak at 1740 cm^{-1} corresponding to the carbonyl ester group, however, the spectrum was not clear enough to give more precise evidence about the possibility of the presence of

by products. The products from the thermal decomposition of TAAS appear to change with the decomposition temperature. This observation is supported by the study of the infrared spectrum of these products at different temperatures (60 - 80°C). Figure (6.5) shows the relative magnitude of the carbonyl frequencies of the products. The product corresponding to complete monomer decomposition shows quite different solubility behaviour from that of the parent acid. It is, for instance, readily soluble in tetrahydrofuran (a known solvent for other poly (∝ - esters) where as tartronic acid is not. The product is soluble in alkaline aqueous solution but begins to precipitate as the solution is neutralised and made acid. Tartronic acid remains in aqueous solution throughout these conditions. The product was found to be sensitive to atmospheric moisture.

The change in product identity upon further heating is probably due to the well known molecular decomposition process of poly - ∝ - esters and may be catalysed by the carboxyl group. A tentative scheme for these reactions is shown below



.... (6.3)

glyoxylic acid

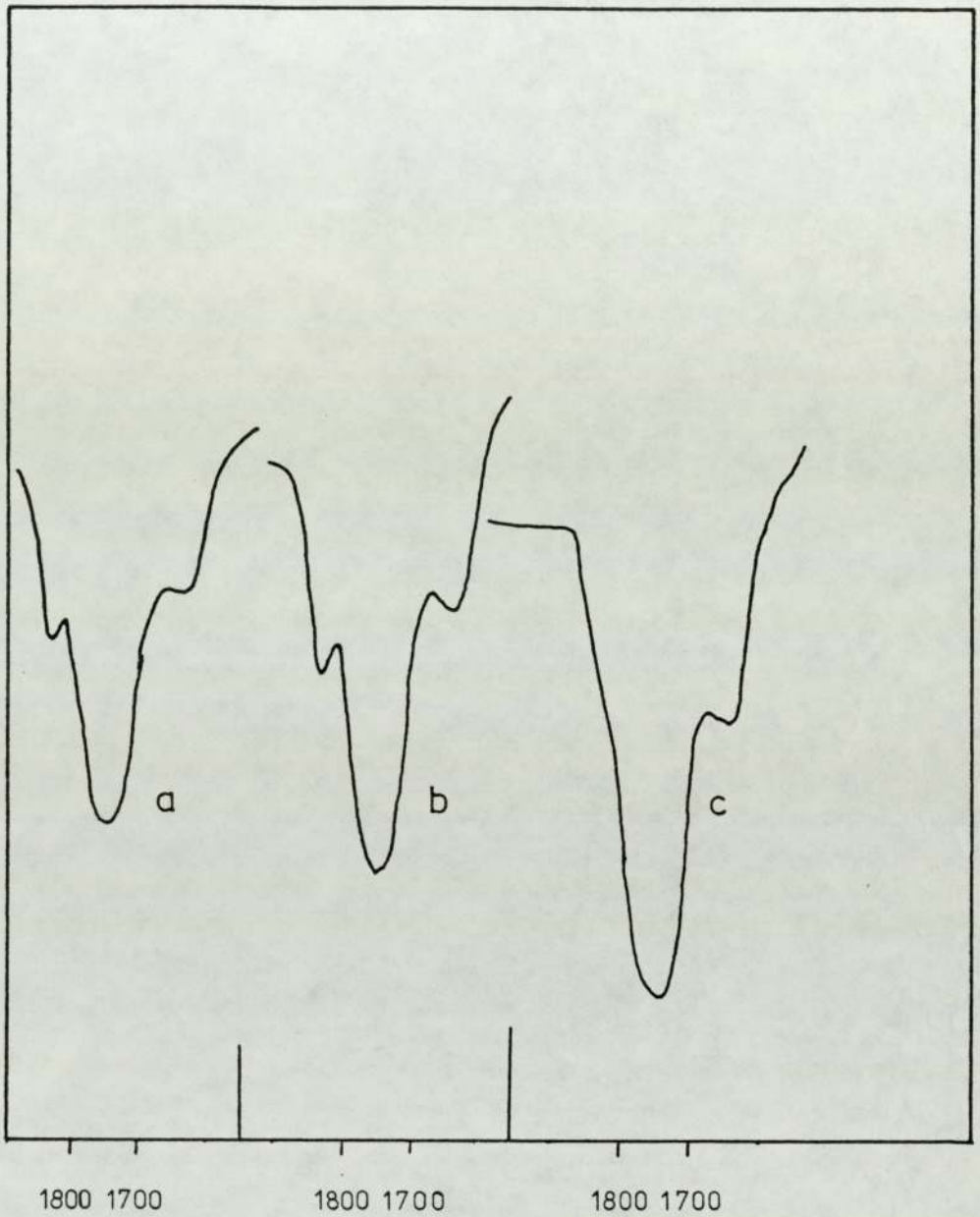


Figure 6.5 Change in Characteristic carbonyl absorption frequency of the products from thermal decomposition of TAAS at different temperature.

a) 60°C

b) 70°C

c) 78°C

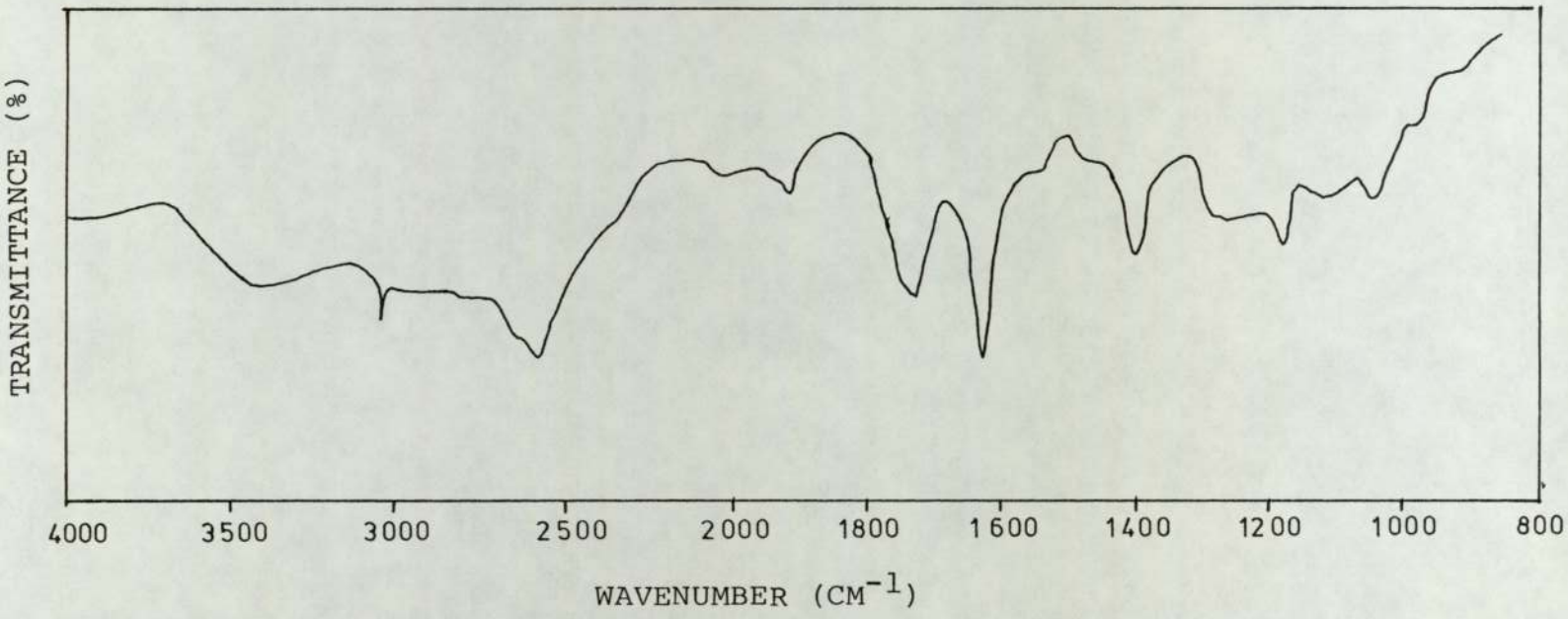
Although this reaction does not occur extensively at the polymerisation temperatures studied some evidence for the existence of glyoxylic acid was obtained by the use of conventional tests for aldehydes (Schiff's reagent, Fehling's solution). Despite the fact that decomposition was relatively slight it was felt desireable to examine alternative room temperature polymerisation techniques.

6.4 Reaction of TAAS with 2,6 - Lutidine

It appeared that in the study of thermal decomposition of TAAS (Section 6.3), the decomposition product contained a by-product in addition to the polytartronic acid. It was decided therefore to examine the use of a sterically hindered tertiary base (e.g. 2,6-Lutidine) in the polymerisation of TAAS in an attempt to obtain polymer at room temperature.

Polymerisation of TAAS with 2,6-Lutidine was carried out in ether at room temperature. Ether was used as the solvent since it is easier to remove it after the reaction is finished. A range of concentrations of 2,6 - Lutidine were used (0.5 M, 1.0 M and 2.0 M) together with a fixed concentration of TAAS (1.0 M). More precipitate was formed when $[M]_o / [I]_o$ was equal to 0.5 probably due to the solubility of the product in basic solutions. The product which was hygroscopic was purified by washing with dry ether and finally cleaned in a vacuum oven. It was stored in a vacuum desiccator over P_2O_5. The infrared spectrum of the product is shown in Figure (6.6). The product is soluble in water and methanol and insoluble in carbon tetrachloride.

Figure 6.6 Infra-red spectrum product obtained from the Decomposition of TAAS by 2,6-Lutidine at room temperature, solvent ether. KBr disc, reference air.



6.5 Copolymerisation Studies - Experimental Results

The thermal copolymerisation of disubstituted (eg. dimethyl, diethyl) anhydrosulphites has been previously studied and it has been established that copolymerisation occurs very successfully especially if the decomposition rates of the anhydrosulphites are similar.

The present work deals with the thermal copolymerisation of tartronic acid anhydrosulphite (TAAS) with ∝ - hydroxy-isobutyric anhydrosulphite (HBAS) and with glycollic acid anhyrdosulphite (GAAS). Although the rates of thermal decomposition of these monomers differ by a factor of more than an order of magnitude, it was decided to examine the possibility of using thermal decomposition as a means of copolymerisation.

Preparation of Copolymers

The anhydrosulphite copolymers were prepared under reduced pressure using Carius tubes, as described in chapter 2. The comonomer solutions were prepared in a dry box, and were then introduced to the tubes by a hypodermic syringe. When the copolymerisation was complete the tubes were cooled in liquid nitrogen and opened. Listed in Table 6.2 are the copolymers prepared together with solvents which were used. This is shown over the page.

Table 6.2

Products from thermal copolymerisation of tartronic acid anhydrosulphite with HBAS and GAAS

Monomer(s)	Mole Ratio	Temp, ^{o}C	Solvent	Nature of product
TAAS + HBAS	1.5:2.0	80	Nitroben-zene	Brown Oil
TAAS + HBAS	1.5:1	70	Anisole	Brown Solid
TAAS + HBAS	1:1	60	Chloro-benzene	Viscous
TAAS + GAAS	1:1.5	75	THF	Brown Gel
TAAS	—	80	Toluene	Brown Gel
TAAS	—	60	Chloro-benzene	Viscous

The products from the above decomposition were characterised by i.r and n.m.r. spectroscopy. The infra-red spectra were recorded from thin-films. All the products gave a peak at 1740 cm^{-1} corresponding to ester carbonyl. The products - which were hygroscopic and stored in the vacuum desiccator over P_2O_5 - were generally more characteristic of poly TAAS than the desired copolymers.

In order to study the effect of TAAS on the thermal decomposition of HBAS, copolymerisation between TAAS and HBAS was carried out in bulk at 70^{o}C using the gas evolution technique described in Chapter 2 and the apparatus shown in Figure (2.4). Figure (6.7) shows the semi-logarithmic plot of the copolymeriastion process. The kinetic result (Figure 6.7) indicate that the copolymerisation process between TAAS and HBAS involves two kinetic parts. Part A of the graph represents the rapid decomposition of TAAS, and the curvature

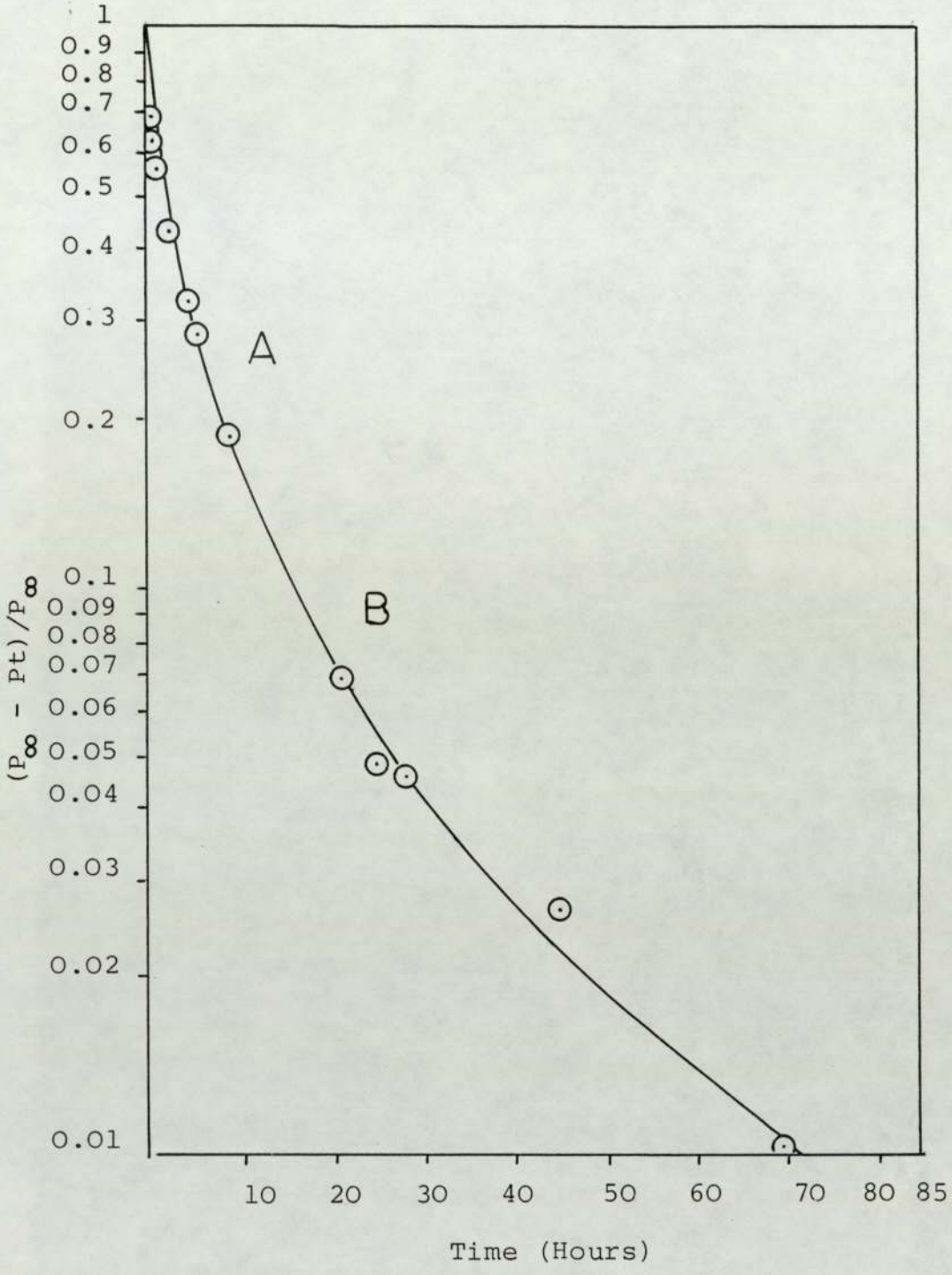


Figure 6.7 Firstorder plot of thermal copolymerisation (Bulk) of TAAS and HBAS at 70.2°C

HBAS/TAAS mole ratio = 1:8

part (B), represents the slow decomposition of HBAS. However, as the monomer (TAAS and HBAS) decomposed thermally with evolution of sulphur dioxide gas, so there are two first order rate constants:

$$TAAS \xrightarrow{k_1} Product + SO_2$$

$$HBAS \xrightarrow{k_1} Product + SO_2$$

From Figure (6.7), the first - order rate constant for decomposition of HBAS in the presence of TAAS is approximately 1.3×10^{-5} $sec.^{-1}$ and this value is similar to the one obtained from thermal decomposition of HBAS in the absence of TAAS (Figure 6.8). The great difference in thermal reactivity of TAAS compared to HBAS explains why the copolymerisation was not effective.

Copolymerisation of TAAS with HBAS was attempted by using 2,6 - Lutidine as inititator. Solution of the monomers in ether were prepared and transferred to subasealed sample bottles. A solution of the initiator in ether was prepared and injected into the monomer solution. After leaving the reaction mixture for two days at room temperature the products were isolated. The results are shown in Table (6.3).

Table 6.3

Copolymerisation product of TAAS with HBAS using 2,6 Lutidine as initiator

$[TAAS]_o$ M	$[HBAS]_o$ M	[2,6- Lutidine] M	Nature of Product
0.5	0.5	0.25	Brown solid
0.5	0.5	0.5	Brown solid
0.5	0.5	1	Brown solid
-	0.5	0.25	White solid

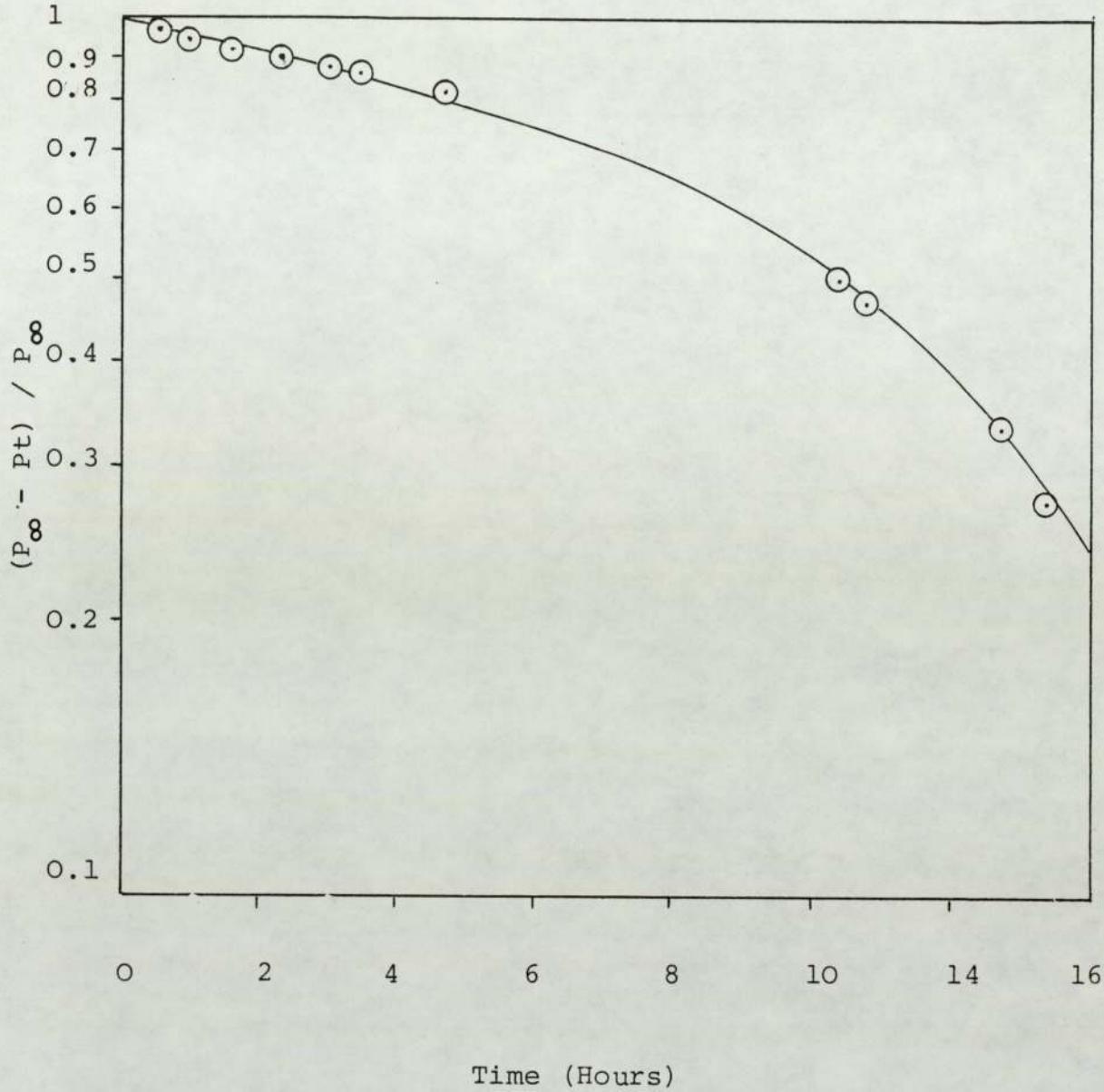
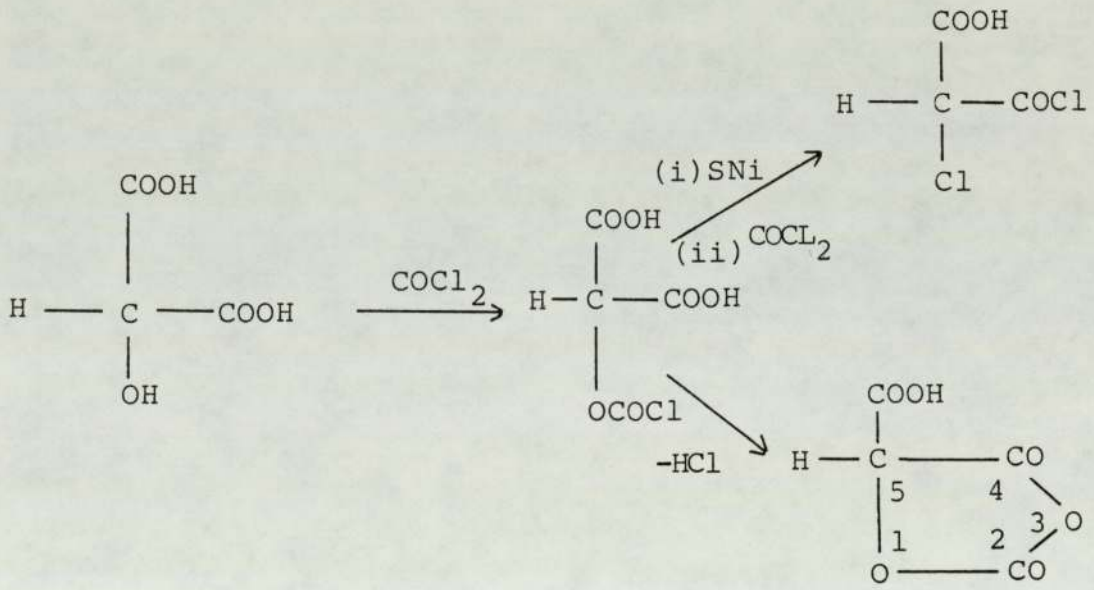


Figure 6.8 First-order plot of thermal decomposition (Bulk) of HBAS at 70.2°C.

The brown solid which was a hygroscopic material was initially characterised by infra-red spectroscopy. The product was setaside for further analysis but in view of the colour of the product it was decided to examine the possibility of making and using the anhydrocarboxylates to obtain purer and more tractable copolymers.

6.6 Synthesis of Tartronic Acid Anhydrocarboxylate (TAAC)

Tartronic acid anhydrocarboxylate (XXX) was prepared from the reaction of tartronic acid (XXXI) and phosgene. In the light of the investigation of previous workers, into the reaction of phosgene with α - hydroxy acids, the reaction path that is suggested for the reaction of phosgene with Tartronic acid is as follows (Equation 6.4).



..... (6.4)

Experimental Details

(i) First Method - :

In a typical experiment, Tartronic acid was dried in

a vacuum desiccator before use following which 5 grams (0.04 mole) of the compound was taken in a conical flask containing 30 mls. of anhydrous ether. Eight (8 grams) of phosgene was passed into 30 mls. of anhydrous ether in a narrow - mounted conical flask and added very slowly to the quickfit flask by a separating funnel, whilst the contents of the flask were continuously agitated by a magnetic stirrer. The temperature of the flask was maintained below 5°C during the addition of phosgene and the reaction was allowed to continue for four days at room temperature. On completion, the excess phosgene and ether were removed under vacuum to leave a white solid. Melting point determination and infra-red analysis showed that the product was tartronic acid itself.

(ii) Second Method : -

Not being able to synthesise the tartronic acid anhydro-carboxylate using ether as a solvent, it was decided to use another solvent, 1, 4, dioxan.

9.9 gm (0.1 mole) of phosgene in 20 ml. 1,4 dioxan was added dropwise to 6gm (0.05 mole) of tartronic acid in 20 ml. 1, 4 dioxan with continuous agitation of the reaction mixture, which was kept in the temperature range 0-5° C. After addition was completed the ice and salt mixture bath was replaced by a 30°C water bath and stirring was carried out for four days. In order to prevent any loss of phosgene by evaporation and any contact with moisture which may be introduced by air, an air condenser filled with cotton wool was used instead of a calcium chloride tube. After the reaction was complete, the excess phosgene and 1,4 dioxan were removed under vacuum at 30°C and white viscous mass

remained which was thought to be tartronic acid anhydrocarboxylate because of its infra-red spectrum and ready decomposition (yielding CO_2) with amines. The yield of this product was 47.5% and the product was soluble in ether and dioxan and insoluble in nitrobenzene, chlorobenzene and decalin. Analysis of the product showed that it was reasonably pure tartronic acid anhydrocarboxylate, having a small amount of chlorine - impurity which was determined by means of potentiometric titration and which was removed by using baked silver oxide as described in chapter 2. Vacuum sublimation of TAAC was carried out as described in chapter 2 without much success. The unreacted tartronic acid ($\sim$12%) was removed by extracting the TAAC with anhydrous ether.

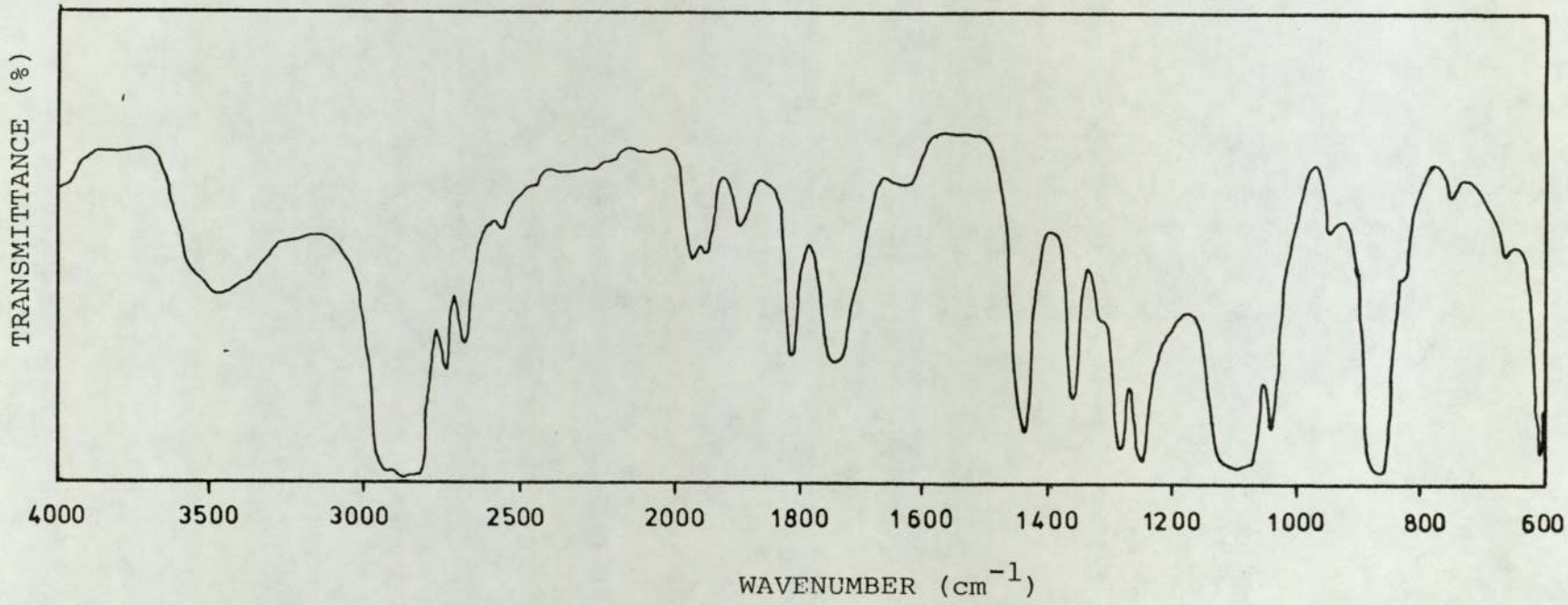
Characterisation of Tartronic Acid Anhydrocarboxylate (TAAC)

Formation of tartronic acid anhydrocarboxylate was characterised mainly by infra-red spectra, n.m.r. and mass spectroscopy together with elemental analysis and gas evolution. Figure (6.9) shows the infra-red spectrum of TAAC (XXX) showing three different carbonyl group stretchings corresponding to two carbonyl groups in the ring [C (2) and C(4)] and one in the carboxylic group attached to the ring at C (5). The peaks in TAAC corresponding to carbonyl groups would be at higher frequencies than that of tartronic acid (XXXI) which appeared as a single absorption band at 1720 ± 5 cm^{-1}. (Figure 6.2). Although in general the formation of the anhydrocarboxylate ring would also be determined by the observation of the disappearance of hydroxyl band at 3400 - 3500 cm^{-1}, in the case of TAAC such an observation would not be expected, since the structure (XXX) still possesses the hydroxyl group. Three absorption bands

Figure 6.9

Infra-red spectrum of Tartronic Acid Anhydrocarboxylate.

The Spectrum was recorded as 10% solution in Dioxan



at, 1895 cm^{-1}, 1810 $\pm$ 5 cm^{-1} and at 1750 cm^{-1} (Figure 6.9) were regarded as consistent with the existence of tartronic acid anhydrocarboxylate in the resultant product.

The mass spectrum of the product was examined and showed a series of peaks corresponding to the fragmentation of the anhydrocarboxylate ring. The peaks observed for TAAC anhydrocarboxylate are shown in Table (6.4).

In addition to the peaks which are presented in Table (6.4), the spectrum shows higher (m/e) peak values. This may be due to the thermal decomposition of tartronic acid anhydrocarboxylate during the process (mass spectroscopy) which involves high temperature, to the low molecular weight polytartronic acid. This is proved because a thermal decomposition product was obtained and confirmed by G.P.C. study (section 6.7).

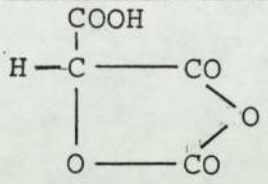
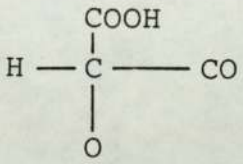
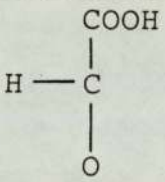
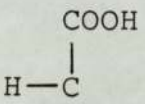
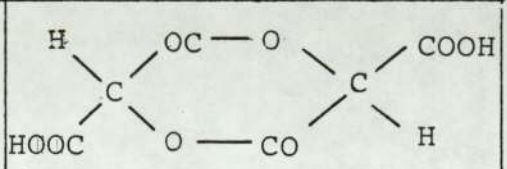
Elemental analysis of tartronic acid anhydrocarboxylate which is shown below

	% C	% H
Expected Result	32.2	1.4
Elemental Analysis Result	31.2	3.7

proved to be unreliable because of the instability of the compounds when exposed to the atmosphere. Quantitative hydrolysis of TAAC to the parent acid(ie. tartronic acid) with volumetric determination of liberated carbon dioxide (94 $\pm$ 2%) provided a reliable estimate of purity.

Table (6.4)

Mass spectrum of tartonic acid Anhydrocarboxylate

m/e	Intensity	Fragment
146	3.3	
102	8.3	
74	28.3	
73	25	
58	73.3	
44	very high	COO^-
32	high	O_2
204	very low	

Because Tartronic acid anhydrocarboxylate (XXX) is a new compound, not previously synthesised the analytical information is compared below (Table 6.5) with the results obtained from anhydrocarboxylate (IX) whose identity is well established.

In view of the difficulties experimental analysis of these compunds the collected results appear to provide good evidence for the identity of tartronic acid anhydrocarboxylate.

Table (6.5)

R^1	R^2	Yield %	m.p. (^oC)	Analysis %C (required)	% H (required)	I.R. ν max (C=O)	CO_2 evolved (% theoretical)
C_6H_5	H	55	54-55	61.9 (60.7)	3.3 (3.4)	1813 (st) 1898 (md)	97^{+}_{-} 2
C_6H_5	CH_3	30	10	60.7 (62.5)	3.6 (4.2)	1813 (st) 1885 (md)	95^{+}_{-} 2
C_6H_5	C_6H_5	53	68-69	72.0 (71.1)	3.7 (4.0)	1808 (st) 1895 (md)	98^{+}_{-} 2
C_6F_5	CH_3	62	64-65	42.6 (42.6)	1.2 (1.1)	1822 (st) 1881 (md)	99^{+}_{-} 2
COOH	H	47.5	< 5	31.2 (32.2)	3.7 (1.4)	1820 (st) 1895 (md)	94^{+}_{-} 2

6.7 Polymerisation of Tartronic Acid Anhydrocarboxylate

The effect of various potential initiators on TAAC was examined. The monomer solution was prepared in the dry box by dissolving in a suitable solvent (eg. THF) and transferring to subasealed sample bottles. In the polymerisation of TAAC, pyridine, 2,6 - Lutidine, 2 methoxy pyridine and lithium

tertiary butoxide were used as initiators. Solutions from these initiators in THF were prepared and injected into the sample bottles containing the monomer solution. After leaving the reaction mixtures to stand for three days at room temperature the products were isolated. Precipitation was observed in each case, which was regarded as a probable indication of the formation of poly TAAC (polytartronic acid). The solvent was then removed and the polymer was washed with ether. Since the polymer was expected to be hydrophilic due to the existence of carboxylic groups attached to the backbone, further drying of samples was carried out in the vacuum oven for several hours at room temperature and kept in the vacuum desiccator over P_2O_5.

In one experiment a diol, decane - 1, 10 - diol (dried in a high vacuum desiccator containing fresh silica gel), was employed in addition to pyridine and 2,6-Lutidine in the hope of doubling the molecular weight of the product. The idea was that in the presence of a diol with tertiary base initiated polymeristion, the chain growth could possibly occur at both ends of the diol which should act as a bridge between two growing chains. The results from this experiment together with the rest are shown in Table (6.6).

Table 6.6

Polymeriastion of Tartronic acid anhydrocarboxylate with various initiators $[TAAC]_o$ = 2.0 M

Initiator	$\frac{[M]_o}{[I]}$	Solvent	Temp.	Time	Nature of Product
Pyridine	4	THF	R.T.	3 days	White gel
Pyridine	4	Dioxan	R.T.	24 hrs.	White gel
lithium t-butoxide	25	THF	R.T.	48 hrs.	White gel
2,6 - Lutidine	4	THF	R.T.	3 days	yellowish green
Pyridine + Decan-1,10-diol (0.005M)	2	THF	R.T.	48 hrs.	White gel
2-Methoxy Pyridine	4	THF	R.T.	48 hrs.	White, very viscous (like a solid)

The Product from Thermal Decomposition of TAAC

Since the basic initiators reacted rapidly with TAAC, it was decided to study the product (polytartronic acid) obtained by the thermal decomposition of the monomer. The polymer was prepared by bulk polymerisa tion at 50°C and separated after the decomposition was complete as assessed using a high temperature kinetic apparatus (Figure 2.4). The product was initially characterised by its ir spectrum and the peak at 1740 cm^{-1} is consistent with polytartronic acid. Table (6.7) shows the G.P.C. result for the molecular weight and molecular weight distribution of the product. The polymer was an off white hygroscopic solid but otherwise similar

in appearance and behaviour to the pale yellow product obtained from thermal polymerisation of TAAS.

Table 6.7

Molecular Weight and Molecular Weight Distribution of Product from Thermal Decomposition (Bulk Polymerisation) of TAAC at 60°C

$\bar{M}n$	2300
$\bar{M}w$	3328
$\bar{M}w/\bar{M}n$	1.45

Copolymerisation of Tartronic Acid Anhydrocarboxylate

Copolymerisation of TAAC with glycollic acid anhydrosulphite (GAAS) and α - hydroxy isobutyric acid anhydrosulphite (HBAS) was attempted thermally and by using suitable initiators, for example lithium tertiary butoxide and 2,6 - Lutidine. Table (6.8)shows the results obtained from this study. All the products were examined by i.r. spectroscopy and show the characteristic change from monomer ($V_{c=o}$ =1820, 1895 cm^{-1}) to polymer ($V_{c=o}$ = 1740 cm^{-1}) in their spectrum.

Table 6.8

Copolymerisation of tartronic acid anhydrocarboxylate

Mole Ratio			Solvent	Time	Temp °C	Initiator	Product
TAAC	HBAS	GAAS					
1	3	-	THF	48 Hrs	60	-	Brown solid
1	-	3.5	THF	48 Hrs	60	-	Brown solid
1	-	3.5	Dioxan	48 Hrs	60	-	Brown Solid
1	-	2	THF	24 Hrs	20	2,6 Lutidine	Brown Solid
1	-	5	Decalin	48 Hrs	40	Lithium t -butoxide	Viscous Product
2	1	-	THF	24 Hrs	20	2,6 Lutidine	Brown Viscous
2	5	-	THF	24 Hrs	20	Pyridine	White Solid

Analyses were attempted by both i.r. and n.m.r. spectroscopy. Whereas i.r. spectra gave satisfactory results for the functional group concerned, however, due to low solubility of the copolymer in common organic solvents, normally used for NMR analysis, it was not possible to obtain successful NMR spectra. The analysis were made more difficult due to the hygroscopic nature of the copolymer. The COOH group peaks in i.r. were indicative of the hygroscopic nature of the product which was therefore difficult to handle. It was concluded that all products were substantially composed of polytartronic acid but that differences in the ir spectra and ease of handling indicated some including of glycollic or α- hydroxy isobutyric acid residues. Further and more detailed attempts at synthesis and analysis must be undertaken

to obtain precise proof of this however.

6.8 Discussion

The major points to be made here relate to the possibility of using the anhydrosulphite and anhydrocarboxylate route in the synthesis of poly - α - esters with a substituent (eg. COOH group) on the α - carbon of the α - hydroxy carboxylic acid(IV) and the effect of such groups on the rate of the polymerisation and copolymerisation of these monomers.

The preparation of anhydrosulphites and anhydrocarboxylates from α- hydroxy carboxylic acids(IV) with functional carboxylic acid substituents presented several problems not previously encountered during the preparation of anhydrosulphites and anhydrocarboxylates from simple aliphatic and aromatic substituted α - hydroxy acids studied by previous workers.

Tartronic acid anhydrocarboxylate (XXX) was successfully synthesised by using 1,4 dioxan as a solvent instead of ether which is known as a common solvent in the preparation of anhydrocarboxylates of α- hydroxy carboxylic acids(IX). 1,4 Dioxan was found to be more advantageous than ether for this particular synthesis for the following reasons

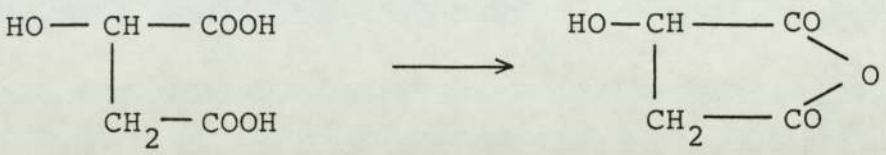
(1) Tartronic acid (XXXI) was completely dissolved in 1,4 dioxan which was not so in the case of ether.

(2) It was believed that the more ready formation of the oxonium ion positively assisted the action of phosgene on tartronic acid.

In contrast the more reactive reagent thionyl chloride reacts smoothly and without difficulty with the hydroxyl

group. As has been mentioned earlier the preparation of cyclic monomers with functional substituents present difficulty and often require group protection.

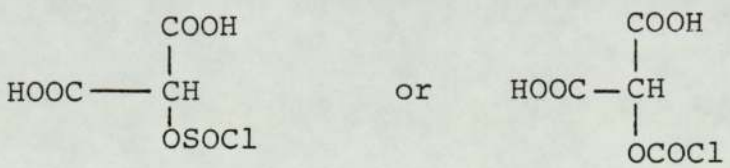
Earlier attempts to synthesise(125) the anhydrosulphite and anhydrocarboxylate of malic acid resulted entirely in the facile dehydration reaction:-



In the present case however no evidence of a similar reaction was observed.

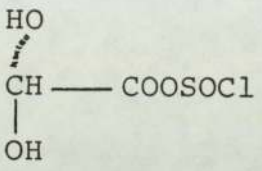
Because of the equivalent of the carboxyl groups in tartronic acid the use of metal e.g. Cu(II) salts as precursor in the synthesis of anhydrocarboxylates and anhydrosulphites do not lead to the very good product. Thus it is impossible to leave one COOH group selectively unreacted.

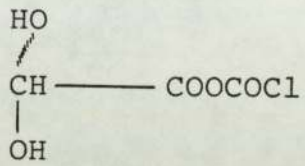
The greater reactivity of the hydroxyl group (compared to the COOH) means that the required chlorosulphinate or chloroformate intermediate can be found in good yield ie.



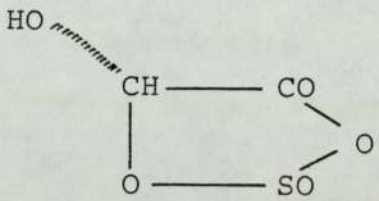
ring closure thus leaving a COOH group unreacted. The only impurities of significance are unreacted acid (which must be avoided by adequate reaction time) and the remaining chlorine containing by-products (which are removed with silver oxide). In contrast, the technique described in chapter 8 for the preparation of a functional monomer containing a hydroxyl substituent requires the selective involvement of one

hydroxyl in the parent molecule (in ring formation). This is achieved in principle by enhancing the reactivity of the carboxyl group in order that this is the site of $COCl_2$/ $SOCl_2$ attack. This procedure which is achieved by forming a metal salt, produces the acyl chlorosulphinate or acyl chloroformate as intermediate.





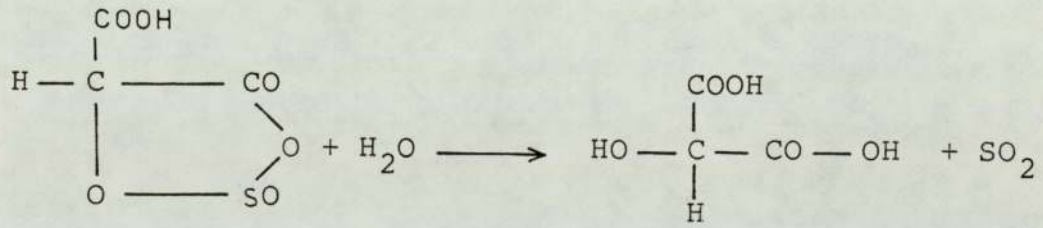
These intermediate rings close to form the five-membered ring leaving the remote hydroxyl unreacted ie.



Again the main expected by products are chlorine containing products that may be removed with a silver oxide suspension. Problems associated with the use of this technique will be discussed in chapter 8. The thermal decomposition of α-hydroxy acid anhydrosulphites has drawn considerable attention. Polymeric products obtained have molecular weights ranging from a few thousands to more than a hundred thousand. The actual molecular weight attained depends on monomer purity, conditions of polymerisation, and the particular monomer used.

The general kinetic and mechanistic aspects of the thermal decomposition of the tartronic acid anhydrosulphite appear to follow the general pattern which has been established for other substituted anhydrosulphites. Firstly,

the reaction of the anhydrosulphite with traces of adventitious moisture yields the parent ∝ - hydroxy acid (Equation 6.5). This reaction which can not be eliminated completely, eventually controls the molecular weight of the final product. Secondly, the anhydrosulphite ring breaks down in a unimolecular process under thermal stress to yield a highly reactive intermediate ∝ - lactone (Equation 6.6). Thirdly, the intermediate reacts rapidly with any available nucleophile (eg. ∝ - hydroxy acid) (Equation 6.7). The general propagation step involves an addition of the ∝ - lactone to the nucleophilic polymer chain end (Equation 6.8) · It is the hydroxyl not carboxyl that propogates.



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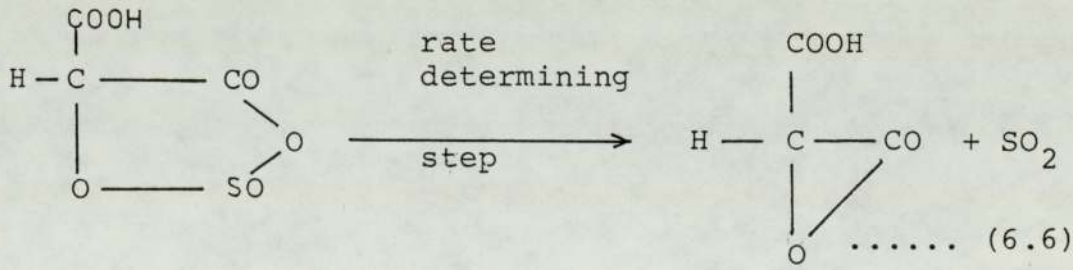

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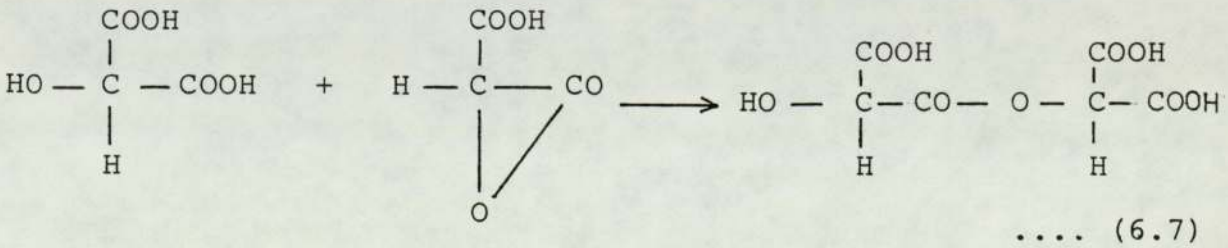

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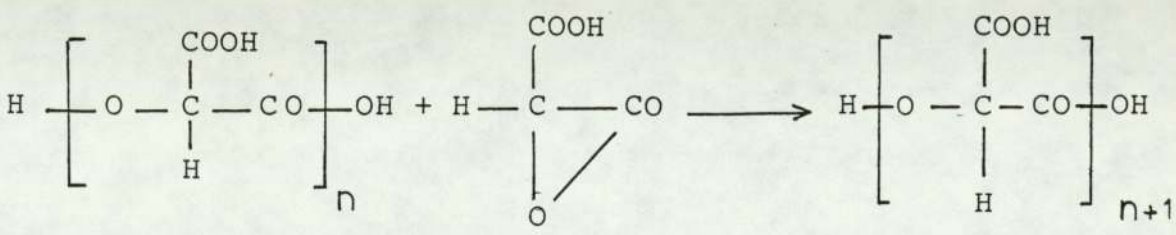
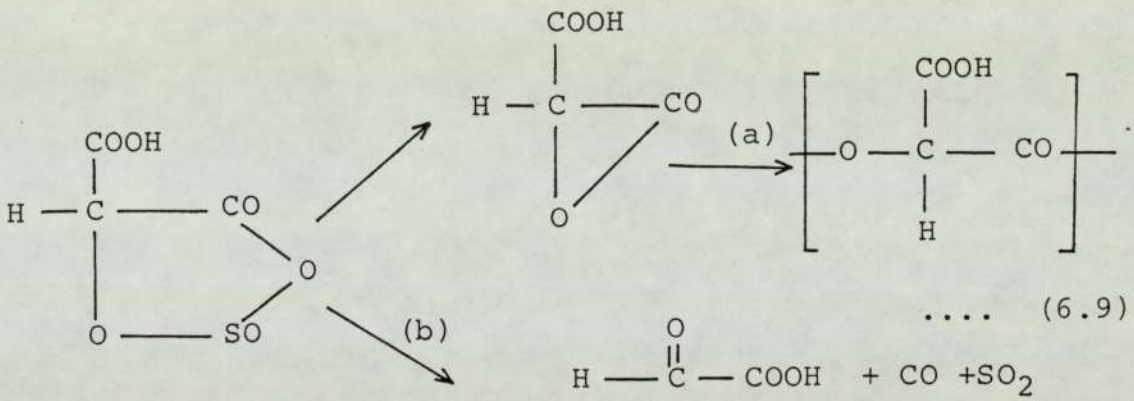


..... (6.8)

Since the decomposition of tartronic acid anhydrosulphite at various temperatures gave good first order decomposition patterns with time, there is no reason to suppose that any of the reaction products, which could have been formed ie. polymer, glyoxylic acid, sulphur dioxide or carbon monoxide (Equation 6.9), accelerated or retarded the reaction rate. Therefore a first order kinetic analysis is assumed to be appropriate and the rate constants obtained are overall first order rate constants.



The possible presence of glyoxylic acid among the decomposition products of tartronic acid anhydrosulphite (Equation 6.9) (as distinct from its formation in polymer decomposition (Equation 6.3)) could be compared to the formation of ketonic species in the fragmentation of the some substituted anhydrosulphites.[46]

The formation of a viscous material from the decomposition suggested that there was no formation of high molecular weight polymeric product. This may probably be the result of termination brought about by the tartronic acid impurities.

As the kinetic data of thermal decomposition of TAAS showed good first order behaviour, it should be possible to

compare the data obtained with that for other monosubstituted anhydrosulphites (VIII) obtained by previous workers. Table (6.9) shows the first order rate constant (k_1), activation energy (Ea), frequency factor (A) and entropy of activation ($\Delta \overset{\ddagger}{S}$) for the decomposition of different anhydrosulphites, (cals are used for comparison).

Table (6.9)

First-order rate constants(k_1), activation energy(Ea), frequency factor (A) and entropy of activation ($\Delta \overset{\ddagger}{S}$) for thermal decomposition of different anhydrosulphites.

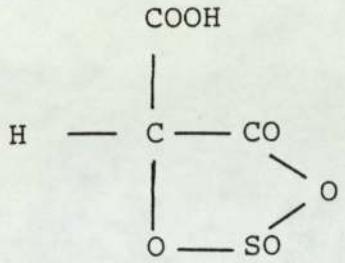
Temp °C	k (sec^{-1})			
	GAAS (a) (VIII, $R^1=R^2$ =H)	LAAS (a) (VIII, R^1=H $R^2 = CH_3$	MAAS (a) (VIII, R^1=H $R^2=C_6H_5$)	TAAS (b) (VIII), R^1=H R^2=COOH)
60			4.0×10^{-4}	
65		0.4×10^{-6}		0.7×10^{-3}
70				1.65×10^{-3}
78.4			14×10^{-4}	3.3×10^{-3}
80	2.0×10^{-6}			
90	5.9×10^{-6}	6.0×10^{-6}	41×10^{-4}	
E(K.cal mol^{-1})	30.4	27.0	18.5	18.00
A (sec^{-1})	6.3×10^{13}	1.1×10^{11}	1×10^{9}	1.9×10^{10}
$\Delta \overset{\ddagger}{S}$ (cal. deg^{-1} mol^{-1})	-	-	-19	-11.7

a) Solvent : Nitrobenzene

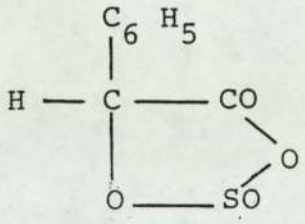
b) Bulk polymerisation

The behaviour of TAAS, as reflected in the various kinetic parameters contained in Table(6.9)is unusual in many ways. The values of k are higher than the other monosubstituted anhydrosulphites. The energy of activation (18.0 K. cal. mol.$^{-1}$) is on the other hand lower than values normally encountered in the thermal decomposition (ie. $\simeq$ 25 - 30 K. cal. mol.$^{-1}$) of anhydrosulphites. Interesting similarities do exist however between TAAS and the anhydrosulphite of mandelic acid (MAAS) which had previously been considered to be unique in its thermal decomposition. High rates of thermal decomposition of anhydrosulphites are usually associated with the presence of two bulky substituents, an observation attributed to the Thorpe - Ingold effect.Both MAAS and TAAS show unusually high rates of decomposition with no steric overcrowding at the C-5 position. In both cases these higher rates of decomposition is associated with a low activation energy (Ea),lower than usual frequency factor (A) and slightly negative entropy of activation ($\Delta \overset{+}{\underset{+}{S}}$). In addition both anhydrosulphites apparently tend to decompose by unusual routes involving carbon monoxide liberation and the formation of carbonyl compounds (benzaldehyde in the case of MAAS and glyoxylic acid in the case of TAAS). The fact that MAAS decomposes almost exclusively by this route whereas it represents a minor pathway for TAAS is probably due to the conjugation stabilisation of some intermediate by the phenyl group.

The general similarities between TAAS and MAAS with respect to kinetic data, can be explained in terms of the similarities between the electron withdrawing group at C - 5



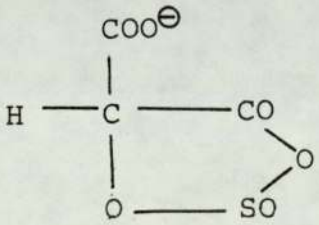
TAAS



MAAS

position of the monomer (ie. COOH group in TAAS and C_6H_5 group in MAAS). The COOH group is more strongly electron withdrawing (higher Taft σ constant) than C_6H_5 group in MAAS, which offers some explanation for the fact that the decomposition of TAAS is more rapid.

The high rates of thermal decomposition of TAAS suggests that the (- COOH) substituent may catalyse the monomer decomposition in a manner similar to that of the tertiary bases. Attempts to prove this hypothesis have so far failed simply because of the difficulty in finding suitable solvents which will enable homogeneous solution of monomer, carboxylic acids and polymer for kinetic experiments to be produced. In one experiment, nitrobenzene was used as a solvent during the study of the thermal decomposition of (TAAS), but unfortunately unusual behaviour was observed which was characterised by formation of a gel material, probably due to the ionization of the substituent carboxylic group to produce



It would have been preferable to use nitrobenzene as a solvent since this was used for the thermal decomposition

of other anhydrosulphites of ∝ - hydroxy carboxylic acid derivatives and it would be easy to make comparison with other anhydrosulphites. Unfortunately TAAS is insoluble in this solvent.

However, from the fragmentation reaction pattern (Equation 6.9), the kinetic results and product analysis, it appears that the normal ring cleavage leading, via an ∝-lactone intermediate to polytartronic acid formation takes place as a major competing (rather than exclusive) first-order reaction [73]. Support for this is found in the appear--ance of a smaller than expected mass peak (M - 64) corresponding to the ∝ - lactone in the mass spectrum of TAAS. Among the peaks in the mass spectrum, there is a peak (m/e = 74) corresponding to the glyoxylic acid (H - $\overset{O}{\overset{\|}{C}}$ - COOH). This supports the suggestion that a competitive fragmentation process (Equation 6.9 b) occurs. These observations indicate that the thermal decomposition of TAAS is not a very useful method to produce a reasonable yield of polymer, since this process requires generation of the ∝ - lactone , which is known to be the reactive species which leads to polymer producing in the thermal decomposition of this type of cyclic monomer. It was for this reason that another method of generating the ∝ - lactone species (ie. tertiary base initiation) was examined.

The experiments which have been carried out demonstrate that the monomer (TAAS) polymerises rapidly in the presence of tertiary organic bases (c.f. chapter 3). In particular the sterically hindered base 2,6-lutidine has been used to enable rapid but controlled polymerisation to be achieved at room temperature in solvents such as diethyl ether which may

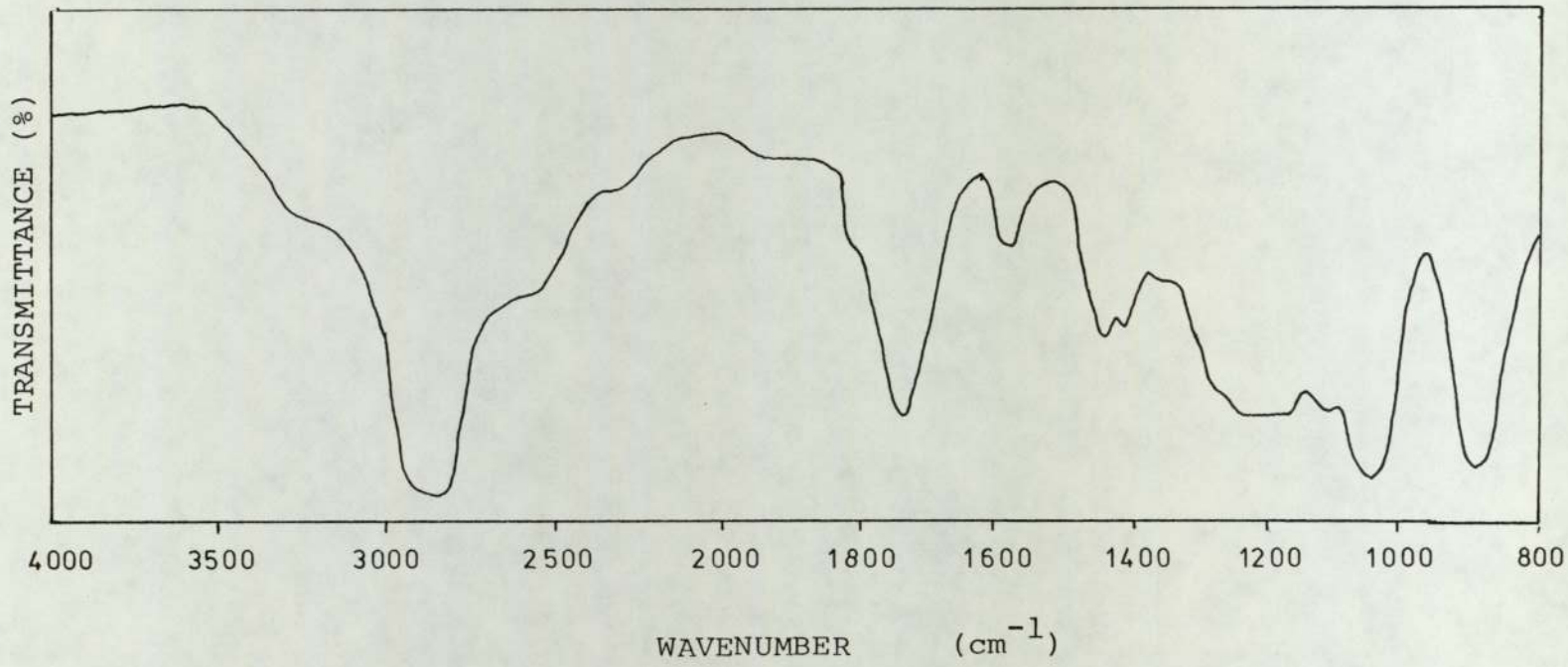
readily be removed when polymerisation is complete.

For the base inititiated polymerisation reactions of TAAC, four different initiators were used namely, Pyridine, 2,6-Lutidine, 2-methoxy pyridine and lithium tertiary butoxide. Infrared spectra of yielded polytartronic acid is shown in (Fig 6.10). Formation of poly tartronic acid may be deduced from the disappearance of absorption bands at 1820 cm^{-1} and at 1895 cm^{-1} for the monomer (Figure 6.9) and appearance of carbonyl peak for the polymer at 1740 cm^{-1}. Among the four initiators used 2,6-Lutidine was found to be the most reactive one where the precipitation occured almost instantly. This was supported from a preliminary investigation by the reactions of $\left[TAAC\right]_o$ = 0.8M with $\left[2, 6\text{-Lutidine}\right]$ = 0.4 M and $\left[2\text{- Methoxy pyridine}\right]$ = 0.4 M in dioxan respectively by using infra-red technique to follow the disappearance of the monomer peaks and appearance of the polymer peak.

The difference in the reactivities of pyridine derivatives may be explained by considering their structures (c.f. chapter 4). It appears from this result that 2,6-Lutidine is more reactive than pyridine due to the higher nucleophilicity of 2,6-Lutidine which is caused by the presence of two methyl groups in the pyridine ring. Comparison with the results presented in chapter 3 (Reaction of Dimethyl anhydrocarboxylate DMAC with pyridine derivatives) shows an interesting difference. In the case of the monosubstituted cyclic monomer (TAAC) the basicity of the tertiary base is more important than steric hindrance. In the case of the disubstituted DMAC the two methyl groups at the C-5 impede the approach of the nucleophile and the steric hindrance of the two methyl groups in 2,6-Lutidine outweighs

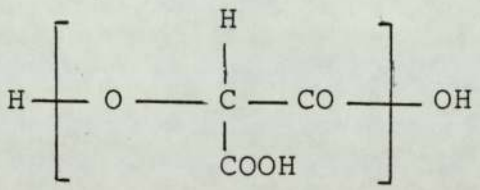
Figure 6.10

Infra-red Spectrum of Product Obtained from the Decomposition of TAAC by 2-methoxy pyridine at room temperature, solvent ether. The spectrum was recorded as 10% Solution in tetrahydrofuran.



their effect on the basicity of the nitrogen. Another observation worth noting was the difference in the colour of precipitates, varying from light brown to reddish yellow. It is difficult to offer an adequate explanation but the phenomenon is well known. Thus the reaction of pyridine with anhydrosulphites is always more rapid than that with the corresponding anhydrocarboxylates and the product is always more coloured and of lower molecular weight.

The expected structure of the polytartronic acid (XXXII) produced by decomposition of Tartronic acid anhydrocarboxylate (TAAC) and Tartronic acid anhydrosulphite (TAAS) may be shown below.

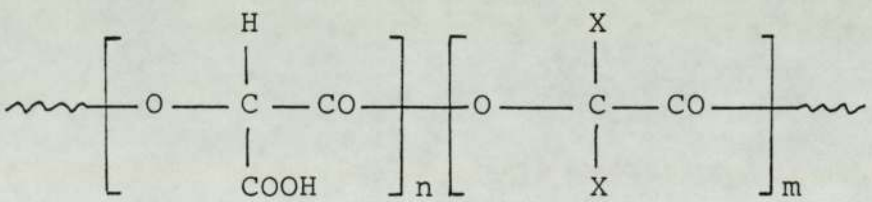


(XXXII)

Because of the physical properties of polytartronic acid (ie. hygroscopic and hydrophilic) and its limited solubility, as mentioned previously it is difficult to subject it to further analysis (for example elemental analysis and nmr). The polymer would be expected to have useful properties for application as a drug carrier since it has both an attachment site (COOH group) and will be biodegradable. The attempts described here to copolymerise tartronic acid derivatives with other monomers are described for several reasons. Because the carboxyl groups make the polymer highly hygroscopic and difficult to handle copolymeriastion with non hydrophilic residues will make the polymer more handleable . This will not affect the usefulness of

the polymer as a drug carrier since it would not be necessary to attach a drug molecule to each repeat unit. In addition variation of the substituent on the α- carbon controls the biodegradability of the polymer and would enable copolymer of controlled biodegradability to be synthesised.

Since the anhydrocarboxylates are more stable than the corresponding anhydrosulphites, copolymerisation reactions of tartronic acid derivatives (TAAC, TAAS) with those of glycollic anhydrosulphite (GAAS) and dimethyl anhydrosulphite (HBAS) were a possible route to copolymer with a small number of carboxylic groups attached to the backbone which could be more useful as a drug carrier than polytartronic acid (XXXII). Some preliminary success has been achieved in copolymerisation of TAAS and TAAC with GAAS and HBAS and the structure of produced copolymer is of the form shown below.

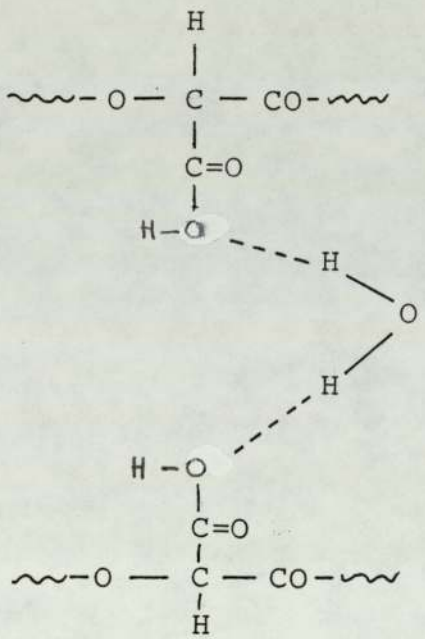


Where X=H in case of using GAAS (V111, $R^1 = R^2 = H$)
and $X=CH_3$ in case of using HBAS (V111, $R^1 = R^2 = CH_3$)
The precise structure will depend upon the concentrations and decomposition rates of the monomers involved.

Polytartronic acid (XXXII)is similar to polyacrylic acid with respect to the carboxylic acid group on the polymer backbone chain. The solubility of polytartronic acid in organic solvents is limited by the presence of the COOH group. Polytartronic acid undergoes reactions characteristic

of a carboxylic acid ie. its aqueous solution is neutralized with sodium hydroxide solution. However this process is of interest since it causes viscosity changes. Ordinarily, aqueous solutions of the poly acids have low viscosities since the polymer is tightly coiled, being only slightly ionized. As sodium hydroxide is added more and more carboxyl groups become ionized. Mutual repulsion of charges forces the polymer chains to uncoil and the extended chains lead to higher viscosity.

Polytartronic acid is a hygroscopic polymer due to the presence of carboxyl groups on the chain which are able to undergo hydrogen bonding with water molecules. The formation of two hydrogen bonds per water molecule are bonded to two adjacent carboxyl as shown below



Because of the hydrophilicity and reactivity of the carboxyl group there are two distinct ways in which polymers and copolymers of tartronic acid could be used in biomedical applications. The first is in the type of copolymer described in this chapter where the type of applications range from drug carriers to modified surgical sutures. Biodegrad-

-able sutures are currently based on polyglycollic acid and suffer from the fact that their degradation does not proceed entirely smoothly. By incorporating a small percentage of carboxyl groups the surface hydrophilicity and water absorbtion of the sutures can be increased and hopefully yield smoother of hydrolytic degradation.

The second type of application is in hydrogel chemistry. Synthetic hydrogels are currently based on carbon backbone (vinyl) polymers that have pendent hydrophilic groups. Crosslinked poly - α - ester copolymers containing hydrophilic groups would constitute a new class of synthetic hydrogels.

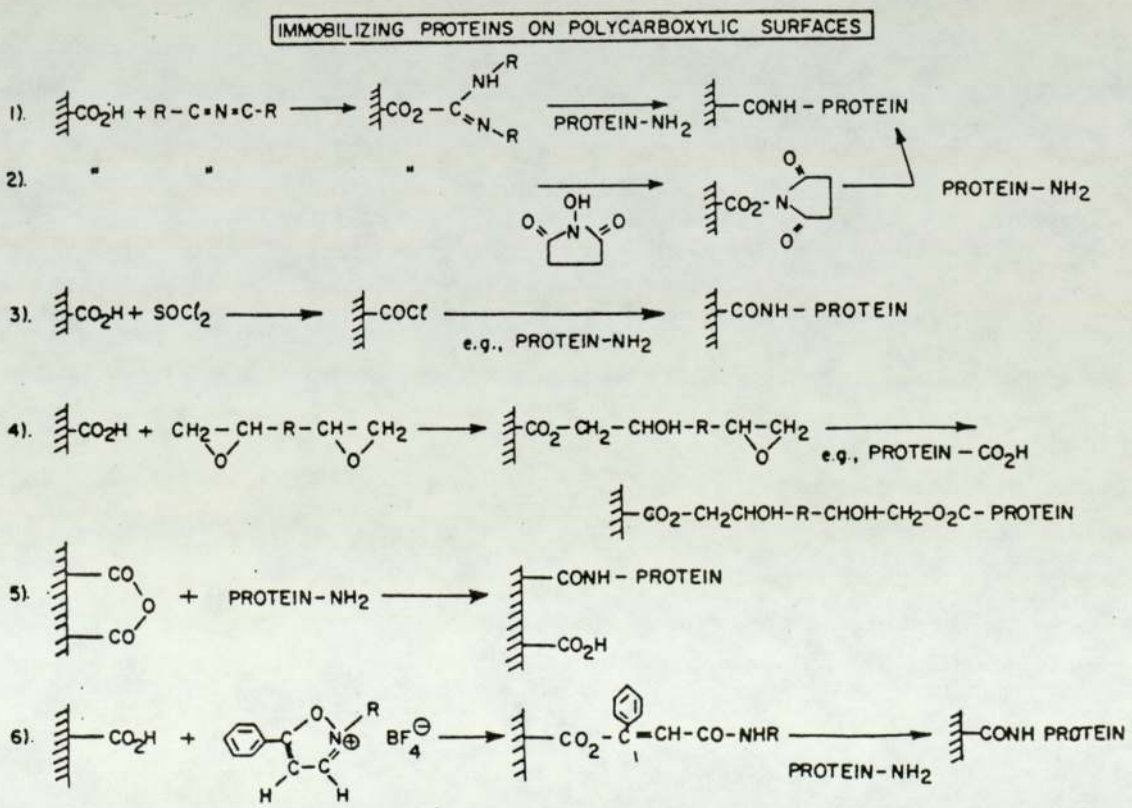
The amount of water absorbed expressed as the equilibrium water content (EWC) is the most significant property of the gel since it has a profound effect on the permeability, mechanical properties , surface properties and biocompatability of the resultant material. In contrast with the hydrophobic nature of most polymers, the existence in a hydrogel network of water having the ability to exchange with aqueous fluid in a biological environment would confer a degree of biocompatability. Recent literature on the factors governing the biocompatability and more general aspects of the biomedical applications of the polymers have been recently reviewed[114]. Hydrogels have been considered as medium for suspending and controlling the release of many physiologically active substances including antibiotics, anticancer drugs, antibodies, enzyme and antibacterial agents. Polymeric drugs may include all agents which upon introduction into a living system cause a physiological response, not only curative but also prophylactic.

A large number of chemical techniques which are particularly applicable for immobilisation to hydrogels have been developed. Figure (6.11) shows chemistries useful for coupling biomolecules to gels containing carbxoyl groups.

Polymeric materials as biologically active agents have potential advantages and disadvantages, as activity may be related to functional groups and to the polymeric nature of the substances [115]. The activity of polymeric drugs can be influenced by molecular weight or molecular weight distribution. Since some of the most interesting active polymers are actually copolymers, modification of the activity can be visualized by the knowledge of copolymer composition, the distribution of the functional groups along the polymer chain, and the stereo chemistry of the polymer.

Figure 6.11* Chemistries useful for coupling biomolecules to gels containing carboxyl groups

* Taken from the reference (116)



Although the work on polytartronic acid derivatives described here is only exploratory it is hoped that it will lead to a more complete examination of these potentially useful materials.

CHAPTER 7

Decomposition of 1,3,2 - dioxathiolane - 4 - one - 2 - Oxide (Anhydrosulphites of α- Hydroxy carboxylic acids) with Polymer Supported Pyridine Catalysts.

The study of reactive polymers is a field which until recently had been largely neglected. There are a number of areas in which suitably modified synthetic polymers have been used as catalysts in recent years. They have been used widely as catalyst or as supports for other catalytic species [117]. The areas of application can be categorised under four main headings:

(i) Catalysis by soluble linear polymers.

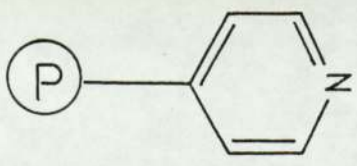
(ii) Catalysis by ion exchange resins.

(iii) Polymer-supported 'homogeneous' metal complex catalyst, and

(iv) Polymer supported phase transfer catalysts.

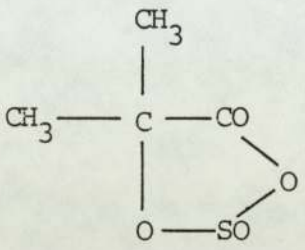
Many naturally occurring processes takes place by such matrix polymerisation, for example the synthesis of nucleic acids and proteins.

The description "supported" refers to the situation where structurally well-defined molecules are attached by specific covalent or ionic bonds to polymeric supports. In order to simplfy chemical equations, a shorthand notatation (XXXlll)has been used. Structure (XXXlll) indicates an organic macromolecular or polymeric support with pyridine pendant group.

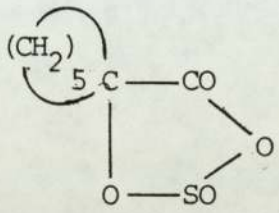


(XXXlll)

The work in this chapter deals with using highly crosslinked polystyrene supported pyridine catalyst in the decomposition of the anhydrosulphites of α - hydroxy carboxylic acid (Vlll) of varying molecular structures (eg. HBAS and Ċhex AS)



HBAS



Ċhex AS

However, this kind of decomposition has also been studied in order to examine the effect of ring strain on polymerisation rates, with particular reference to their ability to undergo ring-opening polymerisation, in terms of both steric and electronic properties of the C(5) substituents.

7.1 Practical Advantages of Supported Catalyst

There are numerous potential advantages in using crosslinked organic macromolecules species by attaching catalysts to insoluble supports:-

(1) The catalyst can readily be removed from batch reactions, often by simple filtration ,

(2) The reaction products are easy to separate from the catalyst and the latter is available for re-use,

(3) Since crosslinked polymers are insoluble and non-volatile, they are non-toxic and odourless. Hence carrying out reactions involving, for example, pyridine compounds on polymer supports is a way of making the reactions environmentally more accept-

able.

7.2 Preparation and Characterisation of the Polystyrene Pyridine Supported Catalyst

The polymer supported catalysts which were used in the present work were supplied by Dr. D. Sherrington of Strathclyde University as beads with a variety of polystyrene based polymeric analogues of pyridine, with varying degrees of backbone substitution and crosslink ratios which are shown in Table (7.1).

Table (7.1)

	No.	% Pyridine Substitution	% Crosslink ratio
Microporous	1	50	2
	2	25	2
Macroporous	3	50	20
	4	25	20

The beads which are shown in Table (7.1) were prepared [118, 119, 120] by free radical suspension copolymerisation using principally styrene and 4 - vinyl pyridine (4 - V P). Figure (7.1) shows the structure of the polymer supported pyridine catalyst which prepared from the above mentioned copolymerisation.

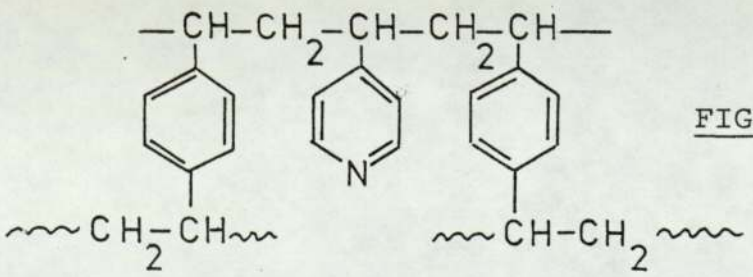


FIGURE 7.1

The beads were dried at 60°C in a vacuum oven for four hours to remove any traces of moisture which might be present (because of the sensitivity of the anhydrosulphite to the moisture) and finally stored in the dry box.

7.3 Infra-red Techniques

The rate of polymerisation of the anhydrosulphites (HBAS and Chex AS) with polymer supported pyridine catalysts was followed using an infra-red technique. The carbonyl absorption of the monomer in the infra-red is sufficiently far removed from that of the polymer, that the rate of dissappearance and appearance of monomer and polymer may be monitored simultaneously by recording infra-red spectra at various intervals of time. The solvent used was chloro-benzene and no absorption of this solvent occurs in the region of study.

The intensity of absorption is given by :

$$\log_{10}\left(\frac{I_o}{I}\right) = \epsilon c l \qquad \ldots\ldots\ldots (7.1)$$

Where I_o is the intensity of the incident light, I is the intensity of transmitted light, ϵ is the molar absorptivity coefficient, l is the path length (constant in this case at 1 cm) and c is the concentration of absorbing species.

The intensity of absorption was measured as absorbance thus :

$$A = \log_{10}\left(\frac{I_o}{I}\right) \qquad \ldots\ldots\ldots (7.2)$$

Equation (7.1) becomes

$$C = A\epsilon^{1} \qquad \ldots\ldots\ldots (7.3)$$

Where ϵ^1 is a constant composed of ϵ and 1. If at any instant concentration of monomer $[M]$ has an absorbance Am, then,

$$[M] = A_m \epsilon^1 \qquad \ldots\ldots\ldots \quad (7.4)$$

The concentration of monomer at zero time is $[M]_o$ and the absorbance is A_o, thus;

$$[M]_o = A_o \epsilon^1 \qquad \ldots\ldots\ldots \quad (7.5)$$

The amount of monomer decomposed at any instant is given by

$$[M]_o - [M] = A_o \epsilon^1 - A_m \epsilon^1 \qquad \ldots\ldots\ldots \quad (7.6)$$

The fraction of total monomer decomposed at any instant is thus

$$\frac{[M]_o - [M]}{[M]_o} = \frac{A_o \epsilon^1 - A_m \epsilon^1}{A_o \epsilon^1} = \frac{A_o - A_m}{A_o}$$

$$\ldots\ldots\ldots \quad (7.7)$$

At any instant during the reaction the following relationship applies ;

$$[M]_o = [M] + [Pr] \qquad \ldots\ldots\ldots \quad (7.8)$$

where $[Pr]$ is the concentration of product. If the absorption is due to the product then at the end of the reaction;

$$[Pr]_\infty = [M]_o \qquad \ldots\ldots\ldots \quad (7.9)$$

and thus,

$$[Pr]_\infty = A_\infty \epsilon^1 = [M]_o \qquad \ldots\ldots\ldots \quad (7.10)$$

The amount of monomer remaining at any time is given by;

$$[M] = A_\infty \epsilon^1 - A_p t^1 \qquad \ldots\ldots\ldots \quad (7.11)$$

where Ap is the absorbance of product formed due to the decomposition of a concentration $[M]_o - [M]$ of monomer.

$$[M]_o - [M] = A_p \epsilon^1 \quad \ldots\ldots\ldots (7.12)$$

The fraction of total monomer decomposed at any time is thus;

$$\frac{[M]_o - [M]}{[M]_o} = \frac{A_p \epsilon^1}{A_\infty \epsilon^1} = \frac{Ap}{A_\infty} \quad \ldots\ldots\ldots (7.13)$$

Considering the rate of polymer formation, the fraction of polymer formed at any instant is given by ;

$$\frac{[Poly]}{[Poly]_\infty} = \frac{A_p}{A_\infty} \quad \ldots\ldots\ldots (7.14)$$

where $[poly]_\infty$ is the final concentration of polymer, $[poly]$ is the polymer concentration at any time during the reaction, Ap is the absorbance of the polymer during the reaction and A_∞ is the final absorbance of the polymer.

If the polymer is formed at the same rate as the monomer is consumed, then the fraction of monomer remaining will be related to the fraction of polymer formed by;

$$\frac{[M]}{[M]_o} = 1 - \frac{[poly]}{[poly]_\infty} = \frac{[poly]_\infty - [poly]}{[poly]_\infty} \quad \ldots\ldots\ldots (7.15)$$

In terms of absorbance, Equation (7.15) becomes,

$$\frac{Am}{Ao} = \frac{A\infty - Ap}{A_\infty} \quad \ldots\ldots\ldots (7.16)$$

A linear relationship for Equation (7.16) is indicative of polymer formation occuring at the same rate as monomer disappearance.

7.4 Polymerisation of HBAS in the Presence of Polystyrene Supported Pyridine Catalyst

α - Hydroxyisobutyric acid anhydrosulphite (HBAS, VIII, $R^1 = R^2 = CH_3$) was prepared from α - hydroxy iso-

butyric acid with thionyl chloride as described in chapter 2 (section 2.6). A known concentration of HBAS in chlorobenzene was prepared in the dry box and a known quantity of supported catalyst (based on the pyridine content) refluxed with chlorobenzene to swell the beads for about one hour. Polymerisation of HBAS in the presence of pyridine supported catalyst was followed by using infra-red spectroscopy techniques (section 7.3) using the apparatus shown in Figure (2.6). After the monomer solution was injected into the round bottom flask (which contains the swollen supported catalyst) through the suba-seal, the resulting mixture was then placed in a water bath at the required temperature ($50^{o}C$). The reaction was carried out under a blanket of dry nitrogen (rather than at reduced pressure) which is used to agitate polymer beads and reactants and to facilitate sample removal. The reaction rate was followed by observation of the disappearance of the carbonyl peak of the monomer ($\nu_{c=o}$ = 1805 cm^{-1}) and the appearance of carbonyl peak of the polymer ($\nu_{c=o}$ = 1735 cm^{-1}). This was carried out by withdrawal of 0.1 ml of the solution at intervals of time for the analysis. Figure (7.2) shows infra-red spectra of a reaction mixture of polymer supported catalyst and HBAS at $50^{o}C$. As the reaction proceeded carbonyl absorption at 1805 cm^{-1} due to anhydrosulphite decreased and ester absorption at 1735 cm^{-1} increased. When this system was kept for a longer period, no change was observed in the strength of absorption at 1735 cm^{-1}. The data of the reaction are presented in the form of a first-order plot in Figure (7.5).

The reaction may be expressed in the form of Equation (7.17)

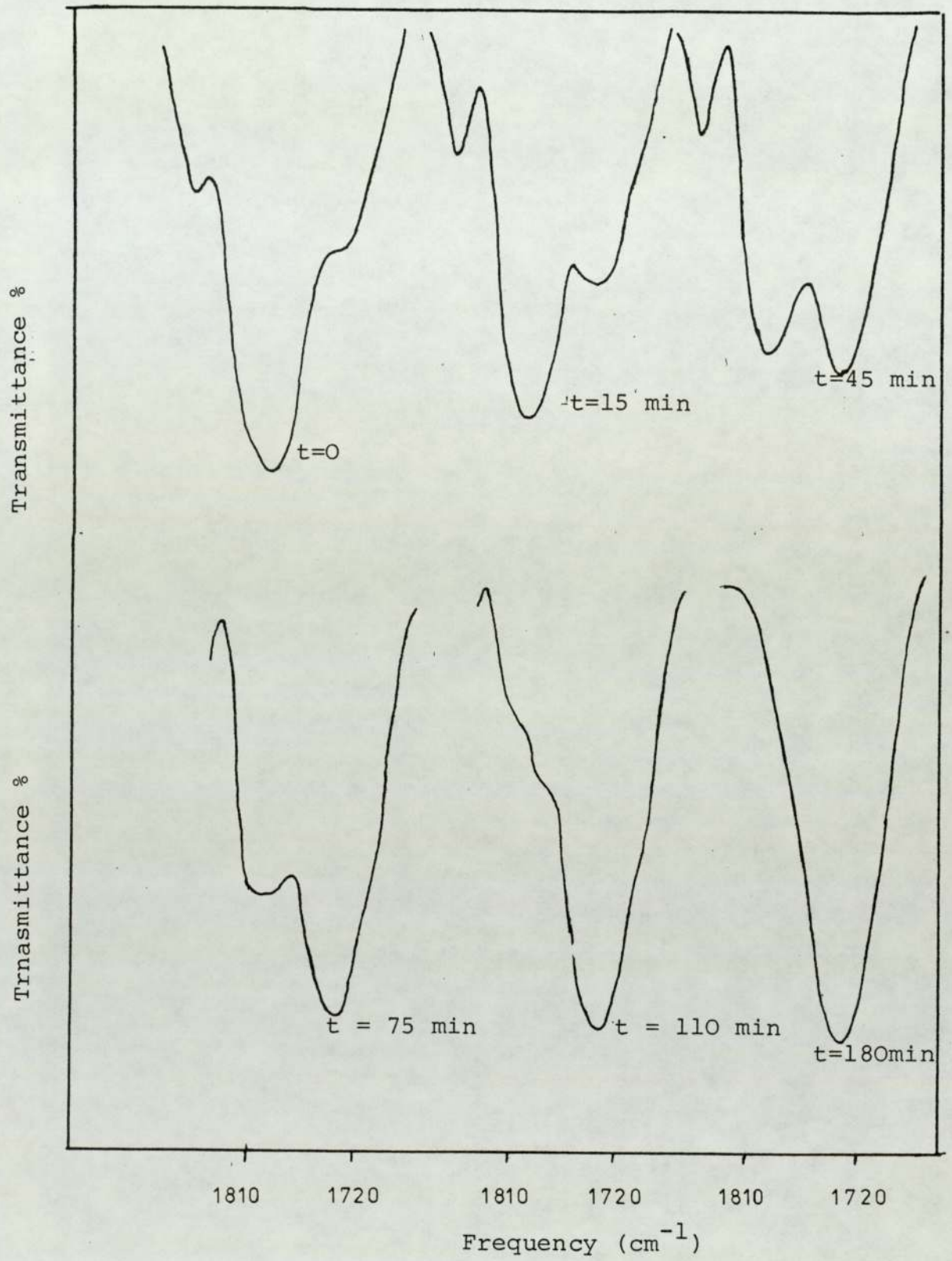


Figure 7.2 Infra-red spectra of samples taken at time t, during the decomposition of HBAS at 50°C in Chlorobenzene using polystyrene supported pyridine catalsyt (2% x link, 50% pyridine), cell thickness = 0.025 cm.

$[HBAS]_o$ = 0.66M , [Catalyst]= 0.69 M

$$- \frac{d[HBAS]}{dt} = \frac{d[SO_2]}{dt} = \frac{d[P]}{dt} = k_1 [Cat][HBAS] \quad \ldots\ldots\ldots (7.17)$$

7.5 Decomposition of Chex AS in the Presence of Polymer Supported Pyridine Catalyst : Rate Measurement and Kinetics of Polymerisation

Cyclohex AS was prepared from cyclohexanol - 1 - carboxylic acid with thionyl chloride as described in chapter 2 (section 2.6). The rate of decomposition of Chex AS with polymer supported pyridine catalyst (No. 1 Table 7.1) was carried out with infra-red spectroscopy by following the rate of polymerisation by growth of the poly - α - ester carbonyl absorption, the reaction was carried out at atmospheric pressure under a blanket of dry nitrogen to facilitate sampling. The apparatus which was used for this purpose is shown in Figure (2.6) . The solution of the monomer in chlorobenzene was prepared in the dry box and then injected into the flask containing the polymer supported pyridine catalyst. The infra-red spectrum of the sample which was removed at intervals of time from the polymerisation flask by hypodermic syringe was measured. Figure (7.3) shows a typical change in absorption of the monomer Chex AS and poly Chex AS with time. The data of the reaction are presented in the form of a first-order plot in Figure (7.5).

The reaction may be expressed in the form of equation (7.18) :

$$- \frac{d[\text{Chex AS}]}{dt} = \frac{d[SO_2]}{dt} = \frac{d[P]}{dt} = k_1 [Cat][\text{Chex AS}] \quad \ldots\ldots (7.18)$$

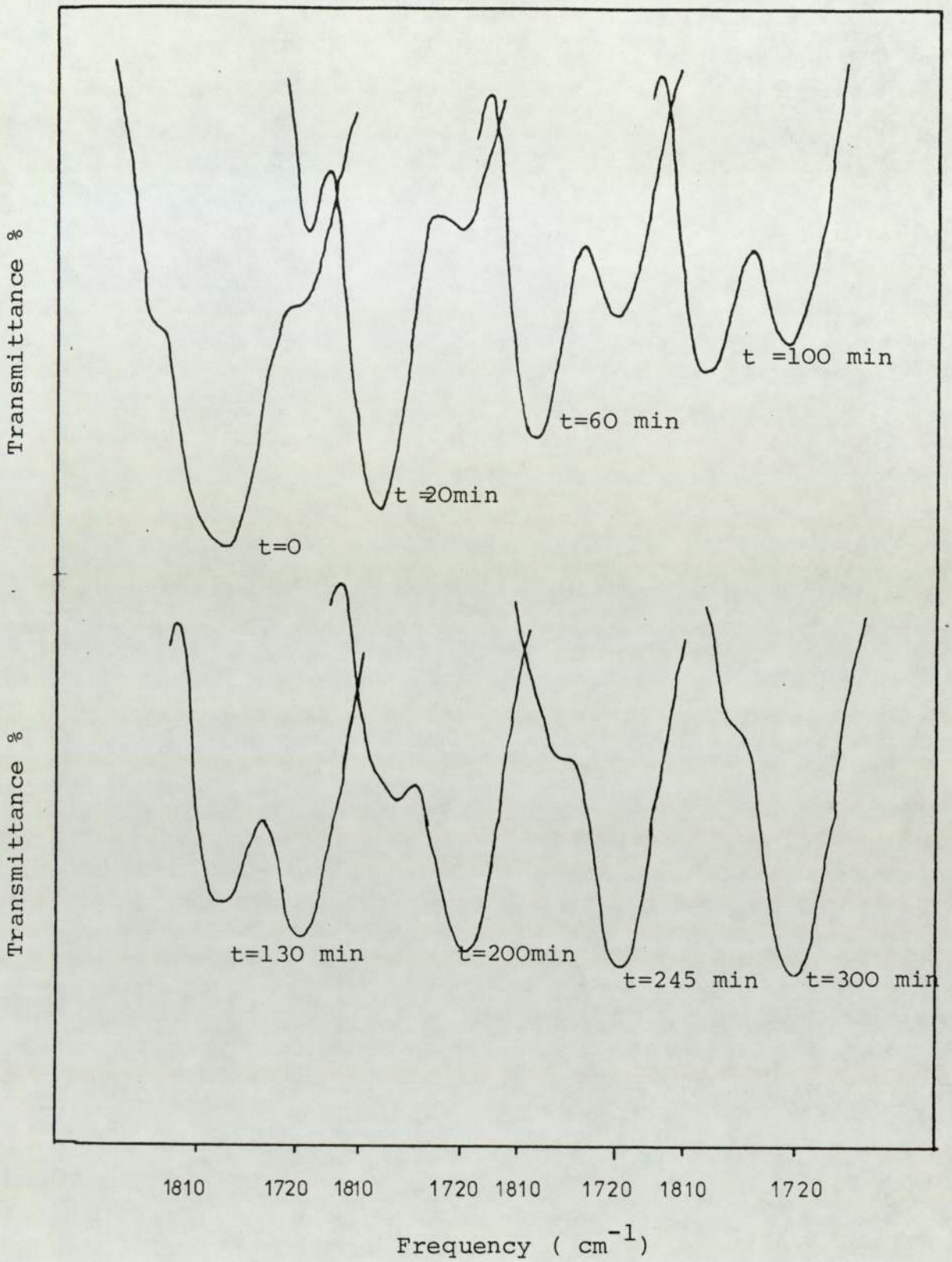


Figure 7.3 Infra-red spectra of samples taken at time t, during the decompostion of Chex AS at 50°C in chlorobenzene using polystyrene supported pyridine catalyst (2% x link, 50% pyridine). cell thickness 0.025 cm

$[\text{Chex AS}]_o$ =0.518 M $[\text{Cat}]$= 0.597 M

7.6 Copolymerisation of HBAS and Chex AS in the Presence of Polystyrene Supported Pyridine Catalyst

This work deals with copolymerisation of HBAS and Chex-AS. Both monomers were prepared as described in chapter 2. The solutions of the monomers were prepared by dissolving in chlorobenzene using the dry box. The polymer beads (No. 1, Table 7.1) were refluxed with a suitable solvent(chloro - benzene) for one hour for swelling the catalyst. The monomer solutionswere injected into the flask (having a rubber seal which permitted the introduction of a syringe without exposing the contents to the atmosphere) by using the apparatus which is shown in Figure (2.6). The rate of polymerisation was carried out using infra-red technique (section 7.3). Samples were taken by hypodermic syringe, quenched and monitored immediately to prevent conversion of any residual monomers (HBAS or Chex AS) to parent acid. The carbonyl absorption of the monomers (1810 cm^{-1}) and the copolymer (1740 cm^{-1}) were monitored as a function of time. Figure (7.4) shows the change in the appropriate region of the infra-red spectrum during the polymerisation. The data of the reaction are presented in the form of a first-order plot in Figure (7.5).

Table (7.2) shows the second order rate constant for the decomposition of HBAS and Chex AS with polymer supported Pyridine catalyst.

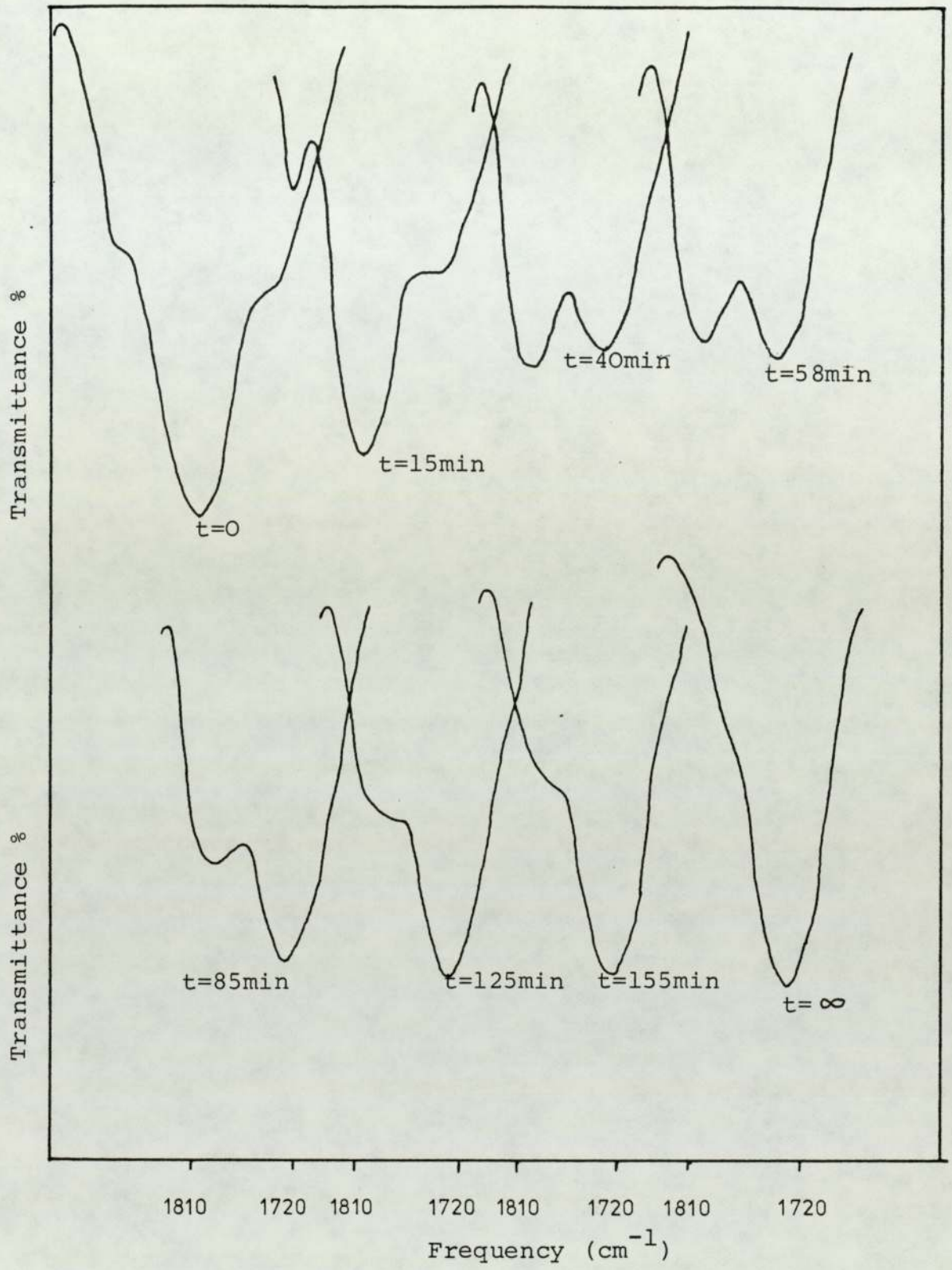


Figure 7.4 Infra-red spectra of samples taken at time, t during the copolymerisation of HBAS and ChexAS at 50°C in chlorobenzene using polystyrene supported pyridine catalyst (2% x link, 50% pyridine), cell thickness 0.025 cm

$[HBAS] / [Chex\ AS] = 0.8$ (mole ratio)

$[Cat] = 0.58$ M

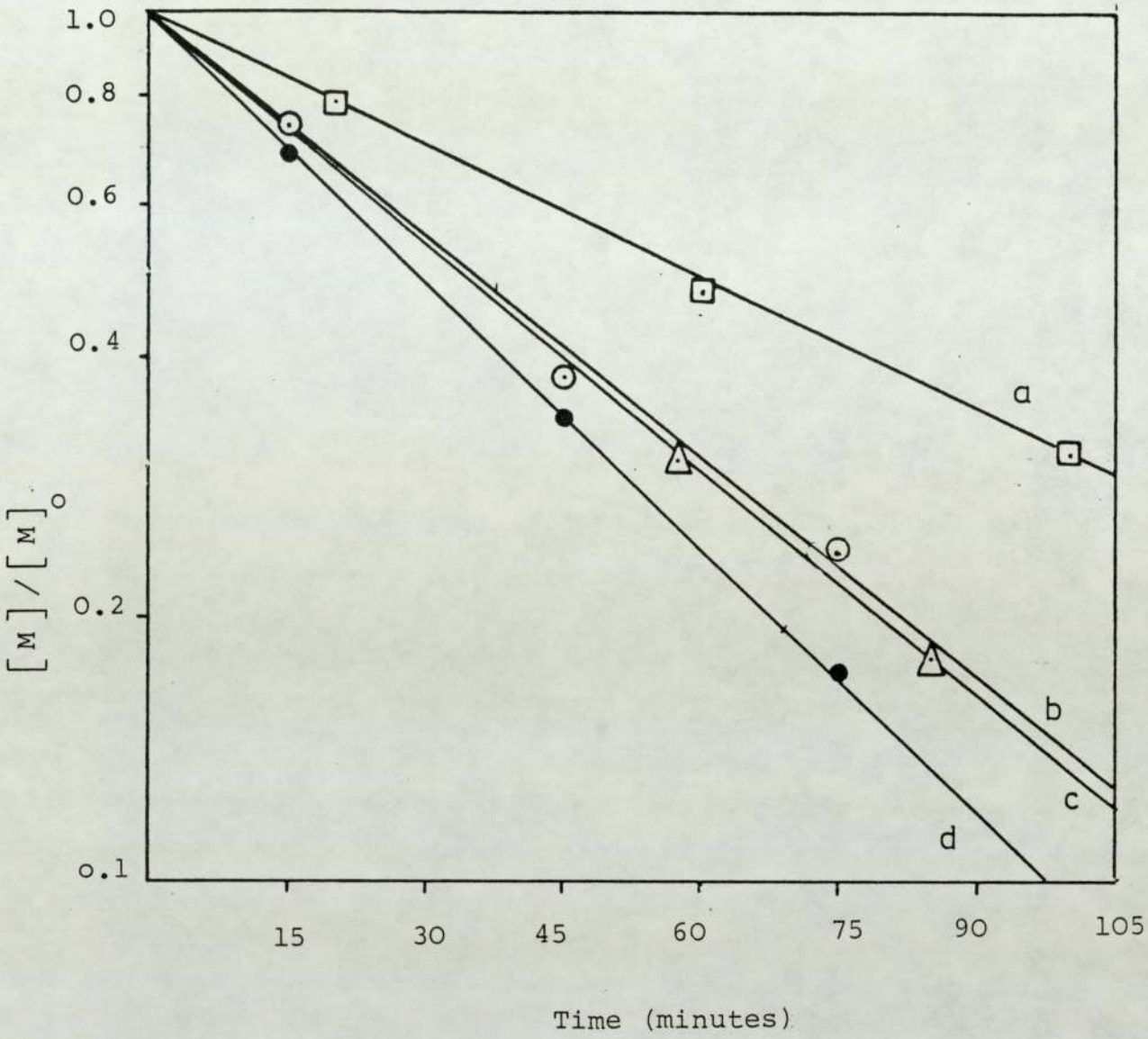


Figure 7.5 First-order semi-logarithmic plot for the decomposition of HBAS and Chex AS with Polystyrene Supported Pyridine Catalyst in Chlorobenzene at 50°C. Reaction carried out in a cell of 0.025 cm thickness.

a) $[\text{Chex AS}]_o = 0.518M, [\text{Py}] = 0.597\ M$

b) $[\text{HBAS}]_o = 0.66M, [\text{Py}] = 0.69M$

c) $[\text{HBAS}]/[\text{Chex AS}]$ mole ratio $= 0.8$ $[\text{Py}] = 0.58M$

d) $[\text{HBAS}]_o = 0.66M$ $[\text{Py}] = 0.69\ M$

Table (7.2)

Second -order rate constant (k_2) for the decomposition of HBAS and Chex AS with Polystyrene Supported Pyridine Catalyst at 50°C in Chlorobenzene

Monomer(s)	$[M]_o$ M	[PY] M	Catalyst No. (Table 7.1)	$k_2 \times 10^{-4}$ l. mol.$^{-1}$ sec.$^{-1}$
HBAS	0.66	0.69	1	4.7
HBAS	0.66	0.69	2	5.66
Chex AS	0.52	0.59	1	3.18
HBAS + Chex AS	0.8 *	0.58	1	5.77

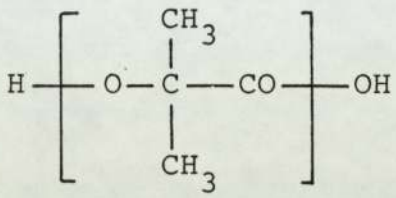
* HBAS / Chex AS mole ratio

7.7 Polymer Characterisation and Molecular Weight Study

The products from the decomposition of HBAS and Chex AS first separately and then as comonomers with polystyrene supported pyridine catalyst were characterised by i.r. and n.m.r. spectroscopy, x-ray and gel permeation chromatography

Poly HBAS was separated after the reaction was completed by precipitating the product using methanol(which is a known non solvent for both homopolymers). The white solid produced was characterised after drying at 40°C. The following absorption peaks were observed in i.r. spectra; 3460 cm^{-1} (ν_{o-H} terminal hydroxyl) ; 2920 cm^{-1} (ν_{c-H}) ; 1750 $\pm$ 10 cm^{-1} ($\nu_{c=o}$); 1110 $\pm$ 10 cm^{-1} (ν_{c-o}). Nuclear magnetic

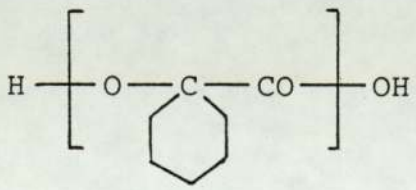
resonance spectra of poly HBAS was recorded in deuterated chloroform. The methyl absorption shift observed was characteristic of the environment given by the structure (X11).



(X11)

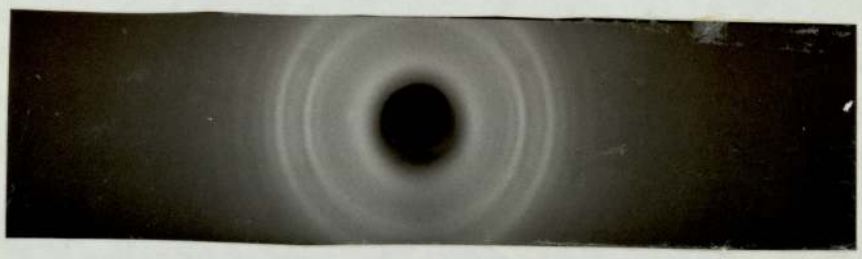
In addition a further absorption was observed which was attributed to hydroxyl proton resonance. The polymer was essentially crystalline in that the appearance of sharp lines was obtained in the X-ray powder photograph (Figure 7.5).

Poly Chex AS and the copolymer from HBAS and Chex AS were precipitated out of the solution by distilling off most of the solvent. Infra-red spectra of poly Chex AS shows the following absorption peaks ; 3450 cm^{-1} (ν_{o-H} terminal hydroxyl); 2920 cm^{-1}, 2850 cm^{-1} (ν_{c-H} of - CH_2 -) ; 1730 cm^{-1} ($\nu_{c=o}$); 1020 cm^{-1} (associated with cyclohexane ring). This evidence with n.m.r. spectra indicate that the poly Chex AS has the structure (XXXlV) poly (1 - hydroxy cyclohexane carboxylic acid).



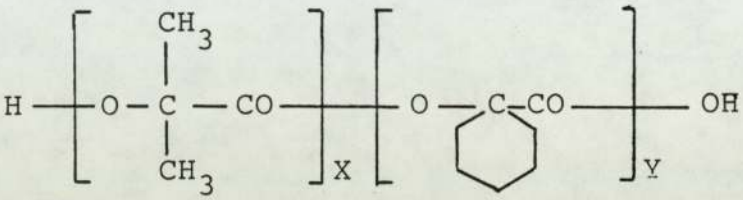
(XXXlV)

FIGURE 7.6



POLY HBAS

The copolymer from HBAS and Chex AS with polystyrene supported pyridine catalyst was characterised as with poly HBAS and poly Chex AS, which indicates that the monomer has the structure (XXXV) where X and Y have values



(XXXV)

depending on the ratio of the monomers and decomposition rates.

Molecular weight and molecular weight distribution of the polymers produced from using polystyrene supported pyridine catalyst are shown in Table (7.3) .

Table (7.3)

Molecular Weight and Molecular Weight Distribution $\bar{M}_w$ / $\bar{M}n$ for the Polymer by Decomposition of HBAS and Chex AS Using Polystyrene Supported Pyridine Catalyst

Supported Catalyst	Monomer	$\bar{M}_n$	$\bar{M}_w$	Highest M_w	$\frac{\bar{M}_w}{\bar{M}_n}$
~2% X link ~50% Pyridine	HBAS	3939	6155	188000	1.56
~2% X link ~50% Pyridine	HBAS	2459	3607	144100	1.47
~2% X link ~50% Pyridine	Chex AS	1642	2168	152000	1.32

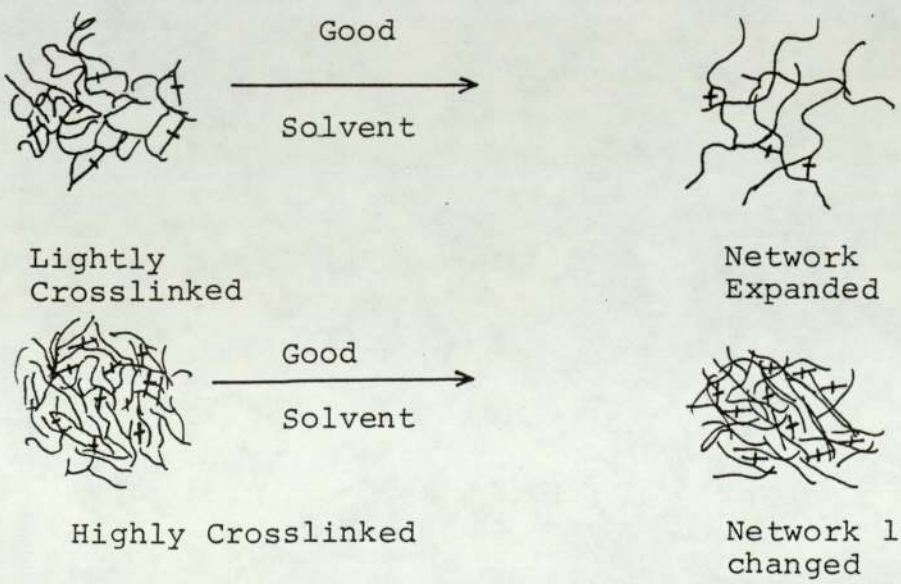
7.8 Discussion

It is clear from the results presented in this chapter, that the polystyrene supported pyridine catalyst was successfully used as an initiator in the decomposition of anhydrosulphites of α - hydroxy carboxylic acid (HBAS and Chex AS), and is able to produce poly - α - ester at controlled rate as might be expected from highly substituted, sterically hindered pyridines. The use of polymer - based catalyst whether in the form of linear (soluble) or crosslinked (insoluble) materials offers a considerable potential improvement in experimental convenience, compared with corresponding low molecular weight initiators as has been discussed in the introduction to this chapter. The tertiary base systems described are attractive for two main reasons. Firstly, the homogeneous reaction of pyridine and its derivatives (c.f. chapter 3) are well studied reactions and known to be simple bimolecular processes. Secondly, 4 - vinyl pyridine which is used in the preparation of these supported catalysts (Table 7.1), is a relatively cheap and readily available monomer carrying an exploitable functional group.

The major points to be discussed here relate to the feasibility of using polymer supported pyridine as catalyst to synthesise poly - α - ester using anhydrosulphite with different substituent on the α - carbon and the effect of such substituents on the rate of anhydrosulphite polymerisation. As mentioned previously, the pyridine reacts very rapidly with anhydrosulphites producing a coloured, low molecular weight polymer. By using a polymer supported pyridine catalyst, however one can control the rate of polymerisation and obtain

a cleaner product.

Crosslinked polymers are not soluble in organic solvents and it was decided to use a suitable solvent (e.g. chlorobenzene) to swell the catalyst beads. The swelling process was achieved by refluxing the beads with the solvent for one hour. The degree of swelling of the beads mainly depends on the nature of the solvent. When a good solvent is added to a crosslinked polymeric network, it can become highly expanded and extremely porous, forming a so-called 'gel'. If the concentration or degree of crosslinking (crosslink ratio) is low (< 2% of backbone substituents interlinked) then such a gel network can consist largely of solvent with only a small fraction of the total mass being a polymer backbone. As the degree of crosslinking is increased, the ability of the network to expand in a 'good' solvent becomes reduced and penetration of reagents to the interior may become impaired. With 'bad' solvents, crosslinked matrices display little tendencey to expand, and movement of reagents within such an interior becomes somewhat analogous to a diffusional process in the solid polymer.



In the present work, chlorobenzene, was chosen as a solvent since it was suitable for both monomers (anhydrosulphites) and for the polymer (in order to separate, with less difficulty the polymer and catalyst).

In the study of the rates of polymerisation of HBAS and Chex AS with supported catalysts, it was difficult to use the gas evolution apparatus and an infra-red technique was preferred.

Tables (7.4) and (7.5) shows the rate constants for decomposition of HBAS and Chex AS respectively with different initiator systems including polystyrene supported pyridine catalyst (present work).

The products (poly - α - ester) produced from the decomposition of HBAS and Chex AS with polystyrene supported pyridine catalyst were isolated from the solvent phase (chlorobezene) rather than from the solid phase (supported catalyst), although the yield of the products were in the range of 70%. This may be due either to the penetration of polymer molecules into the beads or to the growth of the polymer chains taking place within the beads (ie. through the basic functional group). This is because the polystyrene supported catalyst exhibits molecular sieve properties. To confirm this phenomenon, the solid phase (supported catalyst) was subjected to an extraction using tetrahydrofuran which is a good solvent for these poly - α - esters at 40^{o} C, after the polymerisation was complete. Extraction in this way and evaporation of the tetrahydrofuran indicated that there was only a small amount of polymer incorporated in the solid phase. This suggests that the relatively low molecular weight polymer diffuses into and out of the beads with reasonable freedom .Alternatively it may be

Table (7.4)

Rate Constant for HBAS Polymerisation and Decomposition

	Solvent	Temp ^{o}C	Rate-constant	Nature of product
Thermal decomposition[18]	Nitrobenzene	90	6.1×10^{-5} sec^{-1}	Polymer
Benzyl alcohol [18]	Dioxan	40	3.0×10^{-5} l. mol^{-1}. sec^{-1}	Benzyl ∝- hydroxy isobutyrate
Water [18]	Dioxan	40	1.0×10^{-3} l. mol^{-1}. sec^{-1}	Acid
Benzyl amine[18]	Dioxan	40	4.6×10^{-3} l. mol^{-1}. sec^{-1}	Amide
Polystyrene Supported Pyridine Catalyst[a]	Chloro-benzene	50	4.7×10^{-4} l. mol^{-1}. sec^{-1}	Polymer

(a) Rate constant calculated on basin of total availability of pyridine.

Table (7.5)

Rate Constant for Chex AS Polymerisation and Decompositon

	Solvent	Temp. ^{o}C	Rate-constant	Nature of Product
Thermal decomposition[67]	Nitrobenzene	90	5.6×10^{-5} sec^{-1}	Polymer
Thermal decomposition[67]	Nitrobenzene	65	0.21×10^{-5} sec^{-1}	Polymer
Benzyl alcohol[67]	Benzyl alcohol	90	1.22×10^{-5} sec^{-1}	Benzyl 1-hydroxy - cyclohexanoate
Polystyrene supported Pyridine catalyst[a]	Chlorobenzene	50	3.18×10^{-4} 1. mol^{-1} sec^{-1}	Polymer

(a) Rate constant calculated on basis of total availability of Pyridine .

that any polymer formed within the beads is difficult to extract and was not effectively removed by tetrahydrofuran.

The molecular weight values (Table 7.3) of poly - α - ester obtained from decomposition of HBAS and Chex AS with supported catalyst are lower than the values obtained from thermal decomposition methods. Table (7·6) shows the molecular weight values obtained from supported catalyst together with other values from decomposition of HBAS and Chex AS using other methods.

Table (7.6)

Molecular Weight and Molecular Weight Distribution of HBAS and Chex AS from different Initiation Systems

	Monomer	Solvent	$\bar{M}n$	$\bar{M}_w/\bar{M}_n$
Thermal decomposition[18]	HBAS	Nitrobenzene	72,000	1.2
Thermal decomposition[78]	HBAS	Chlorobenzene	100,000	1.25
Thermal decomposition[67]	Chex AS	Nitrobenzene	12,250	1.31
Lithium t- butoxide[93]	HBAS	Decalin	1390	1.62
Polystyrene Supported Pyridine Catalyst	HBAS	Chlorobenzene	3939	1.56
Polystyrene Supported Pyridine Catalyst	Chex AS	Chlorobenzene	1642	1.32

One aim of this section of the study is to compare the contributions of ring strain, and also steric and electronic effects in the decomposition of HBAS with the spiroalkyl anhydrosulphite (Ċhex AS). The results are presented in Table (7.2). It has been previously shown [101] that in the thermal decomposition studies of HBAS and Ċhex AS, the cyclohexane ring has similar effects to that of two methyl substituents. This suggests, as expected, that little ring strain exists and that in terms the Thorpe-Ingold effect the contributions of two methyl and one spiro cyclohexyl group are comparable. The difference in rate constants for reaction with the supported pyridine catalysts is more marked however, the value for HBAS being 50% greater than that for Ċhex AS. This probably reflects the greater steric hindrance of the spiro cyclohexyl group in a bimolecular reaction involving charge transfer complex formation.

It is evident from the results (the kinetic and analytical) presented in this chapter together with those in chapter 3 that the mechanisms involved in the decomposition of anhydrosulphites in the presence of supported catalyst are different from those involved in the thermal decomposition of these compounds. The characteristic features of the supported pyridine catalyst initiated reaction, may be summarised as follows:

(i) The reaction is first-order with respect to monomer and shows some dependence on the amount of solid catalyst present.

(ii) The rate of appearance of polymer is equal to the rate of disappearance of monomer (as shown by

infra-red analysis).

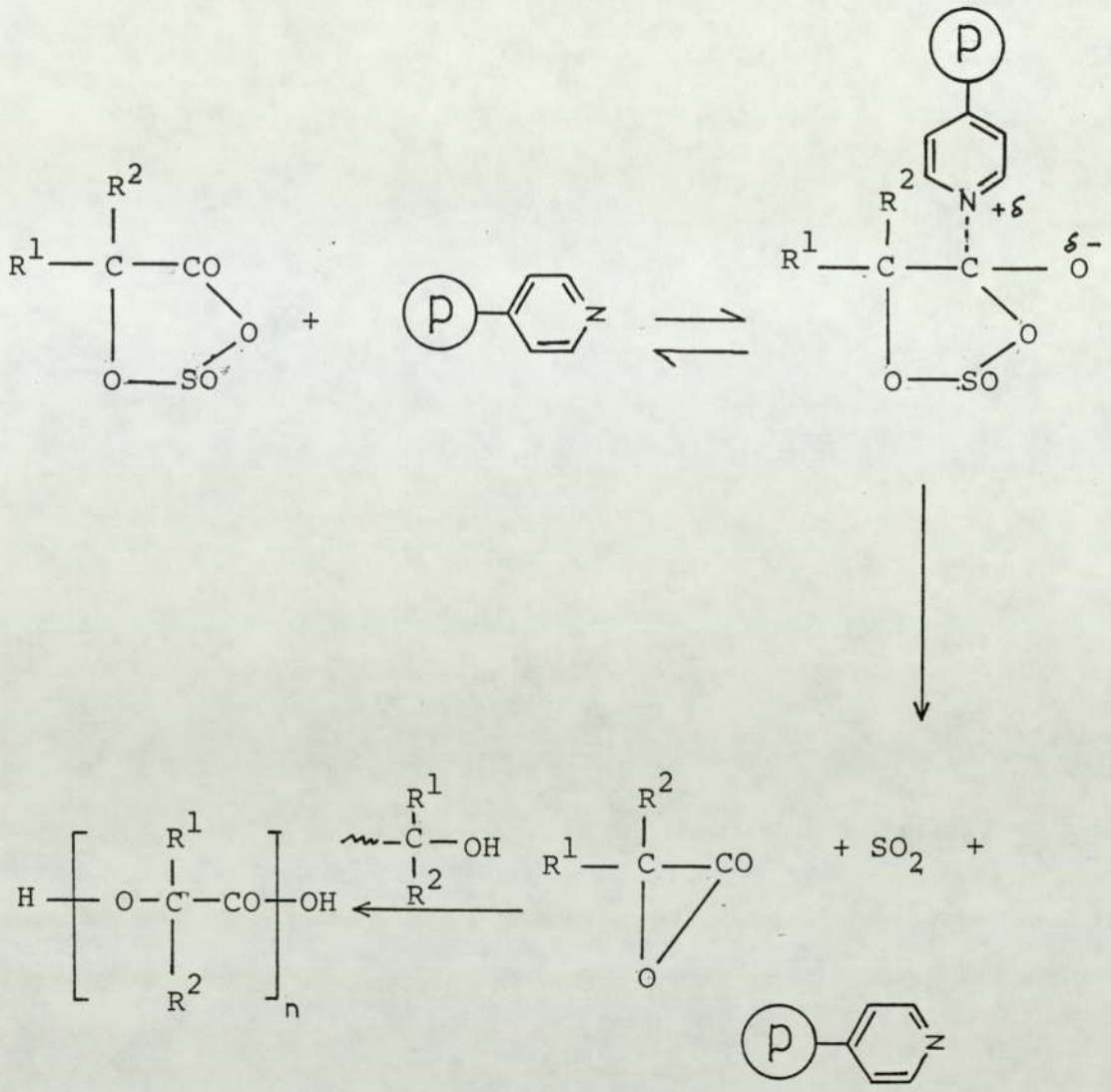
(iii) Anhydrosulphites are decomposed more slowly as the substituent is changed from alkyl to spiroalkyl.

(iv) The molecular weight of the poly - α - ester product seems to be dependent on the kind of the catalyst (i.e. on the pyridine %). This may be related to other factors such as impurity level however.

(v) The poly -α- ester products from the decomposition of anhydrosulphites with polystyrene supported pyridine catalyst are clean and white, whilst when using pyridine itself (homogenous reaction), the products are brown (c.f. chapter 6).

(vi) The structure of the resultant poly - α - ester is indistinguishable from the structure of polymers obtained by thermal polymerisation. In particular the polymer chains contain carboxylic and hydroxyl group.

The sequence of reactions leading to the formation of polymer may be formulated by following the proposed mechanism which is based on that presented in Chapter 4. It involves the fragmentation of the anhydrosulphite ring in the presence of polymer supported catalyst to form a charge transfer complex. This complex is broken down to form sulphur dioxide with the formation of a species (α - lactone) which is capable of taking part in a polymerisation reaction. The reaction sequence is shown in Equation (7.19), in which the α - lactone takes part in a rapid chain propagation step with the terminal hydroxyl group of a polymer chain.



..... (7.19)

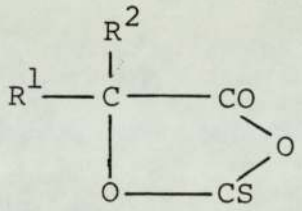
This type of catalyst has great promise for copolymerisation of functional monomers but unfortunately arrived too late in the project for detailed evaluation. There are many aspects of their behaviour that are of interest, in particular the site of formation of polymer and its ability to diffuse in the gel network.

CHAPTER 8

Novel Functional Monomers: Additional Synthetic Studies

8.1 Attempted Synthesis of Thio-anhydrocarboxylate of α - Hydroxy Carboxylic Acid

Thio - anhydrocarboxylate(XXXVI) are another group of ring structures which may be classified as cyclic esters of carboxylic acids containing α - functional groups.



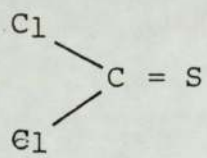
(XXXVI)

The aim of this work is the synthesis of the 2 - thioxo-1,3 - dioxolan - 4 - ones (XXXVI) from the corresponding α-hydroxy carboxylic acid (IV), mainly from glycollic acid (IV , $R^1=R^2=H$) and α - hydroxy isobutyric acid(IV , $R^1=R^2=CH_3$). A great deal of research has been carried out into the preparation and purification of other kinds of cyclic esters of α - hydroxy carboxylic acid, ie. anhydrosulphites (VIII) and the anhydrocarboxylates(IX). Since these monomers are able to undergo polymerisation (as mentioned previously) which involves concurrent extrusion of a small molecule, for example SO_2 (from the anhydrosulphite) and CO_2 (from the anhydrocarboxylate), therefore it has been suggested that a possible synthetic route to the formation of poly - α-ester

would be via a thioanhydrocarboxylate (XXXVI) .

The potential value of another type of ring of this sort lies in copolymerisation work. This would be especially true if it proved possible to copolymerise these rings with anhydrosulphites and anhydrocarboxylates, and thereby overcome the problems associated with the effect of substituents on ring reactivity. The ideal situation would arise if one type of ring with two methyl substituents has similar reactivity to another type of ring with one hydrogen and one carboxyl substituent.

No information is available concerning the mode of synthesis and purification of these thio-anhydrocarboxylates but since the general method for the preparation of anhydrosulphites (VIII) is by the action of thionyl chloride on the corresponding acid (or acid derivatives) and the anhydrocarboxylates (IX) are prepared by the action of phosgene on the corresponding acid, one can envisage that the thio-anhydrocarboxylate ring could be formed from the reaction of an α - hydroxy acid with thiophosgene (XXXVII) which is



(XXXVII)

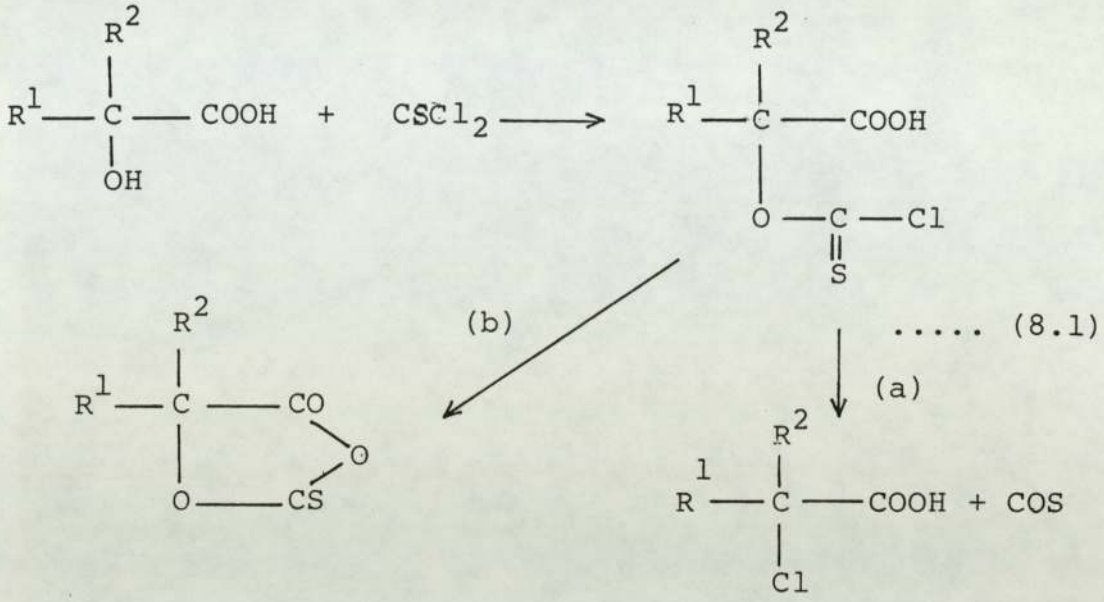
structurally similar to phosgene and thionyl chloride.

There are two methods which may be used in the synthesis of thio-anhydrocarboxylates.

(i) Action of thiophosgene with α- hydroxy acid :

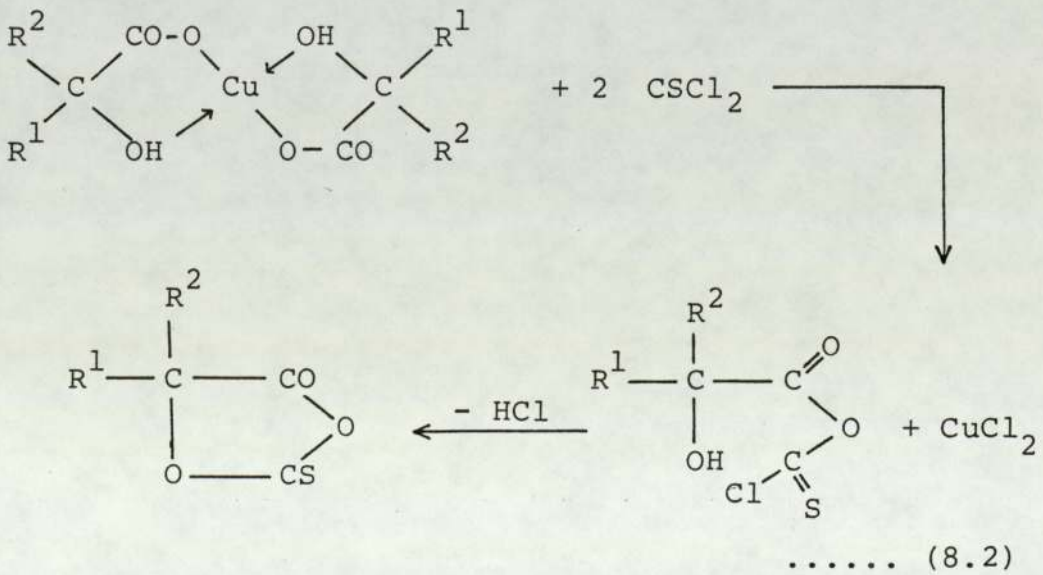
This method would perhaps lead to formation of an α - chloro substituted acid (Equation 8.1 a) by means of an

internal nucleophilic substituent or by cyclisation to form the required ring compound (b).



(ii) Action of thiophosgene on the copper salt of ∝-hydroxy carboxylic acid:

In order to minimise reaction (a), Equation (8-1), a successful modification of the synthesis of the thio-anhydrocarboxylate might be to proceed via the copper salt of the acid (Equation 8.2), which was shown to be successful in the preparation of anhydrosulphites.



8.1.1 Attempted Reaction of Cupric Glycollate with Thiophosgene

0.05 mole of dry cupric glycollate (prepared as in chapter 2) was slurried in 150 mls anhydrous ether and 0.1 moles (11.5 gms) thiophosgene (which was dissolved in anhydrous ether) was added dropwise over a period of two hours maintaining the temperature below $0^{o}C$. On completion of the addition of thiophosgene the mixture was allowed to warm up to room temperature and the reaction continued for one week, by which time the copper salt had become brownish yellow, the colour characteristic of anhydrous cupric chloride. The mixture was filtered and the cupric chloride washed with anhydrous ether. The ether and unreacted thiophosgene was stripped from the filtrate under vacuum, a yellowish solid remained behind. This solid was assumed to be a mixture of glycollic acid and the required glycollic acid thioanhydrocarboxylate contaminated with thiophosgene. To the solid, anhydrous toluene was added, the vessel was shaken and left for a day. This left a solid and an orange solution. The solution was decanted off, after drying, an infra-red spectrum of the solid indicated that there was only acid present. The resulting brown solution was vacuumed off at $40^{o}C$ to remove excess toluene. After evacuation brown viscous oil was left and infra-red apectra indicates that there is no glycollic acid thioanhydrocarboxylate being formed.

8.1.2 Reaction of α - Hydroxyisobutyric Acid and Thiophosgene

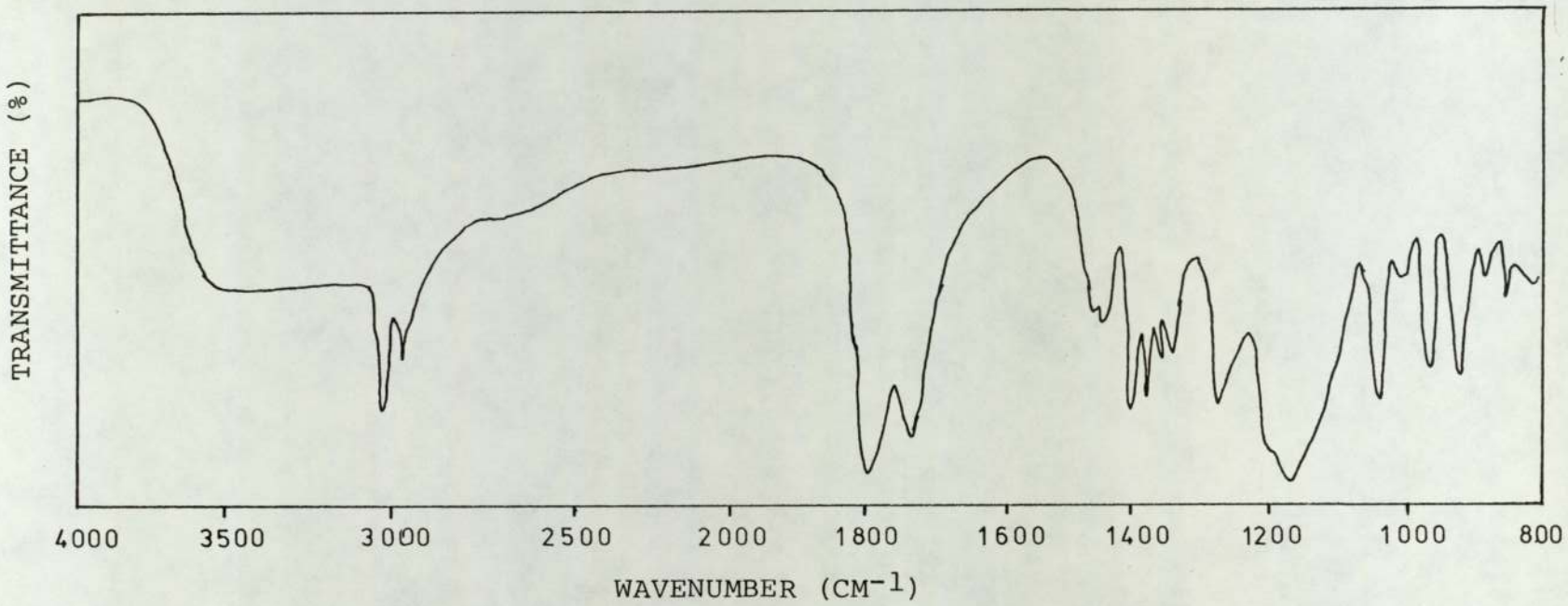
In a typical experiment 0.05 moles of α - hydroxy-isobutyric acid was slurried in 50 mls of anhydrous ether. 0.1 moles thiophosgene which was dissolved in ether was added dropwise over a period of an hour, maintaining the temperature below $0^{o}C$. On completion of the addition of thiophosgene the reaction was continued for four days at room temperature after which time it was stopped and the solution evaporated under reduced pressure to remove ether and unreacted thiophosgene. After evacuation a brown oil was left in the flask. This brown oil reacted with benzyl amine produced the efferevescence associated with break-down of the ring and evolution of gas.

Characterisation

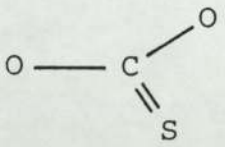
The product from the reaction of α - hydroxy isobuty-ric acid with thiophosgene, dimethyl thio-anhydrocarboxylate (DMTA, XXXVI $R^1=R^2=CH_3$) was characterised by infra-red and mass spectra. The infra-red spectrum (Figure 8.1) shows two strong obsorptions in the carbonyl region at 1740 cm^{-1} and 1800 cm^{-1}. The peak at 1800 cm^{-1} is due to the ring carbonyl group C(4) of the thioanhydrocarboxylate (XXXVI). The peak at 1740 cm^{-1} was attributed to carbonyl of the acid impurity. The presence of this impurity could be due to the hydrolysis of the ring by traces of moisture or because of hydrolysis during the infra-red spectrum recording (since the method used for infra-red analysis was the thin film method). There is

FIGURE 8.1

Infra-red spectrum of dimethyl thioanhydrcarboxylate. The spectrum was recorded as a thin film using KBr plates, the reference cell was air.

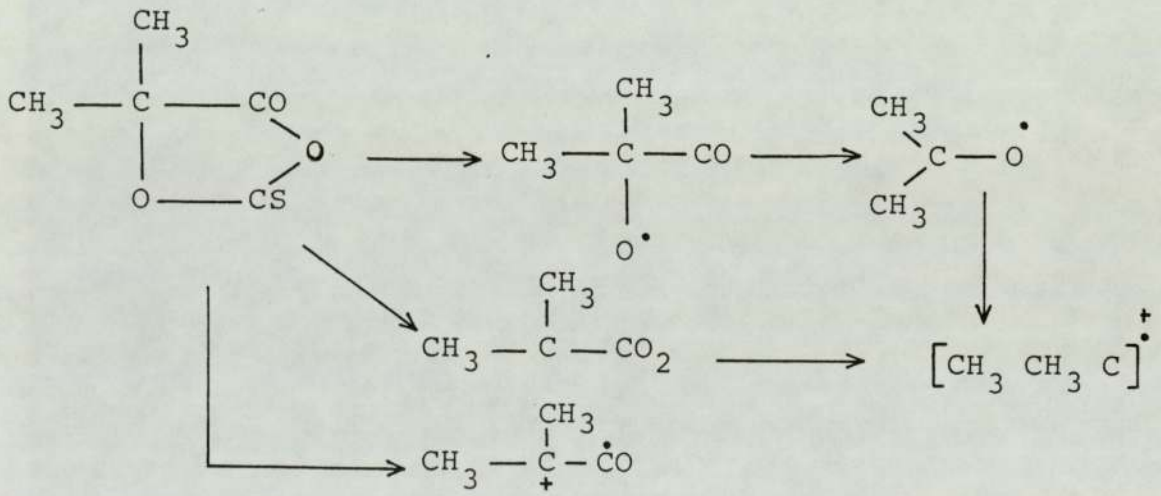


another peak at 1280 cm^{-1} which is due to the stretching of the C=S bond. The appearance of slightly high wave-number is due to the environment of the bond as the carbon is bonded to two oxygens



which will reduce the electron density at the C=S bond.

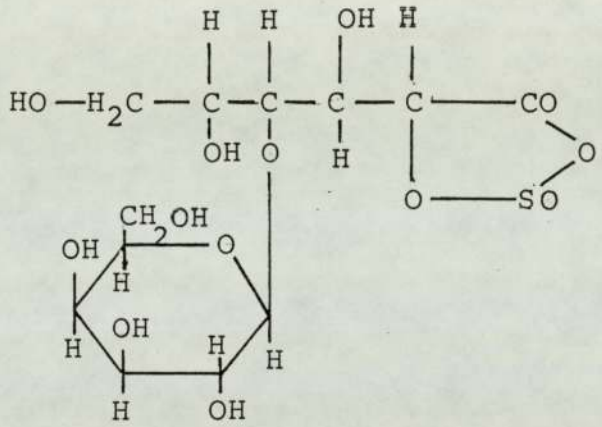
Mass spectral analysis of DMTA shows peaks at 86, 58, 60 and 28, from which it can be assumed that it is possible that the α - lactone, acetone, carbonyl sulphide and carbon monoxide will produced from the breakdown of DMTA, as shown below.



Thioanhydrocarboxylate spectra however, showed no trace of a top mass peak corresponding to the unfragmented ring, M. In this respect, the anhydrocarboxylate of α - hydroxy acid(IX) shows a molecular peak[75] whilst the anhydro-sulphite (VIII) does not[66].

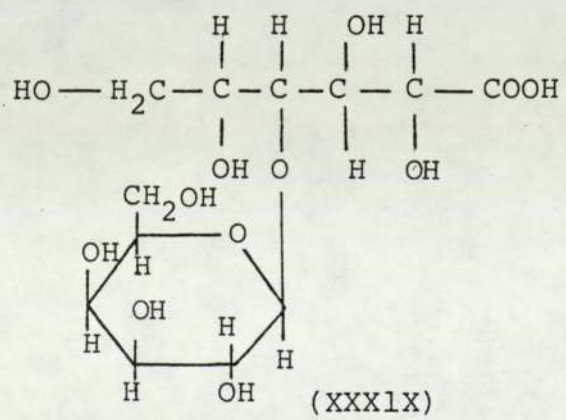
8.2 Attempted Synthesis of Lactobionic Acid Anhydrosulphite (LBAS)

The aim of this work is to continue the work that is presented in chapter 6 which involves preparation of monomers with useful α - functional groups. In this section, attempts to synthesise lactobionic acid anhydrosulphite (XXXVlll),



(XXXVlll)

have been examined in order to introduce another kind of functional group which contains a carbohydrate unit and hydroxyl groups. The α - hydroxy carboxylic acid which is used in this synthesis is lactobionic acid (XXlX) which was available commercially. It was difficult to obtain Lactobionic acid (XXXlX) in the anhydrous state, as



(XXXlX)

it contains hydroxyl groups which make the acid hydrophilic. Therefore it was suggested that the preparation of a metal salt of lactobionic acid would provide a suitable method for LBAS preparation.

8.2.1. Preparation of Copper (11) Salt of Lactobionic Acid

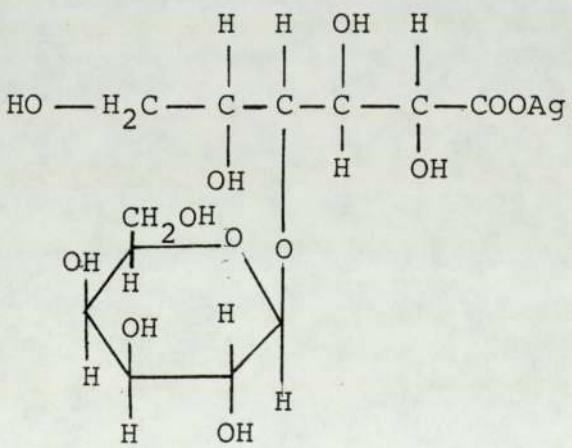
0.5 Moles lactobionic acid was dissolved in a minimum quantity of water. The solution was treated with 0.880 ammonia solution to neutralization. This solution was heated to boiling point to remove excess ammonia and the solution concentrated as much as possible. 0.25 Moles cupric chloride dissolved in a minimum amount of water was then added with continuous stirring. The mixture was allowed to cool but no precipitate appeared. By dropping this solution into a tenfold excess of methanol a greenish precipitate was obtained which was filtered off, washed with methanol and dried. An infra-red spectrum of the dried cupper salt showed a band centering at 1620 cm^{-1} indicating the presence of a carboxylate anion. In addition, there is a peak at 1740 cm^{-1} which was attributed to the carbonyl peak of the acid (similar to the peak which was observed in i.r. spectrum of lactobionic acid). Elemental analysis of the product is shown below:

	%C	%H
Theoretical	37	5.7
Experimental	34.2	5.9

Because of these results which suggest incomplete conversion it was decided to use another metal salt, for example, silver salt of lactobionic acid as a precurser to synthesise LBAS.

8.2.2. Synthesis of Silver Salt of Lactobionic Acid

0.014 Mole (5gm) of lactobionic acid was dissolved in 10 ml of water. The solution was treated with ammonia solution to neutralization. This solution was heated to boiling point to remove excess of ammonia. 0.014 Mole (2.38gm) of silver nitrate dissolved in a minimum amount of water was added with continuous stirring. The mixture was allowed to cool but no precipitate appeared. By dropping this solution into a tenfold excess of methanol a white precipitate was obtained which was filtered off, washed with methanol and dried. An infra-red spectrum of the dried silver salt showed a band centering at 1600 cm^{-1} indicating the presence of a carboxylate anion (structure XXXX) with no residual carboxyl peak at 1740 cm^{-1}.



(XXXX)

8.2.3. Reaction Between Silver Salt of Lactobionic Acid and Thionyl Chloride

0.02 mole silver salt of lactobionic acid was taken and slurried in 30 mls of anhydrous ether. 0.03 moles of thionyl chloride dissolved in a little ether was added dropwise. The reaction mixture being kept at $0^{o}C$. After 2 days, the mixture was filtered and the ether and excess thionyl chloride stripped off under vacuum. The residual brown oil which produced was stored under vacuum in the dry box.

Characterisation

The product from the reaction between thionyl chloride and silver salt of lactobionic acid reacted vigorously with benzyl amine at room temperature with the evolution of sulphur dioxide. This is a characteristic reaction of anhydrosulphites. The infra-red spectrum of the parent compound was not clear, with broad rather than sharp peaks, this was probably due to the fact that this anhydrosulphite is highly reactive and decomposed in the moist atmosphere during the i.r. spectral analysis. There is a peak at about 1740 cm^{-1} which is typical of an ester group. The presence of this group was presumably due to a reaction between the substituent hydroxyl groups and the anhydrosulphite ring. The infra-red spectrum also showed a strong hydroxyl absorption and there was a peak at 1200 cm^{-1} which could be attributed to the the S=O group in the anhydrosulphite ring (XXXVIII).

Although this is only a preliminary step in the sucessful isolation of pure cyclic derivatives of lactobionic acid it does demonstrate the feasibility of the method.

Lactobionic acid anhydrosulphite has been synthesised

using both the copper(11) salt of lactobionic acid and the silver salt of lactobionic acid.

More success has been achieved using the silver salt due to its ease of drying and greater ease of formation.

The anhydrosulphite compounds (eg. LBAS) are mostly liquids, but they are difficult to purify by distillation due to the decomposition of the anhydrosulphite during the process. The case of the anhydrocarboxylate of lactobionic acid should be easier to deal with than the anhydrosulphite, because the former could be prepared as a solid and purified by vacuum sublimation.

8.3 Discussion

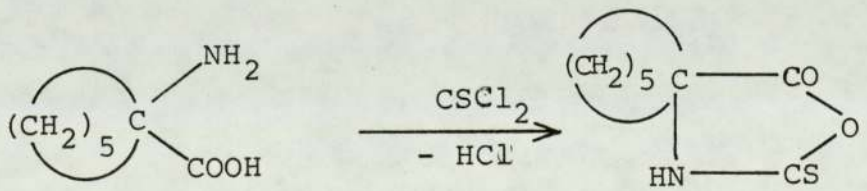
The difficulties experienced in the preparation of glycollic acid thioanhydrocarboxylate, (section 8.1.1), are illustrated by the amount of impurities, which predominantly arise from the presence of the parent acid. The difficulties are made worse by the absence of any literature concerning thioanhydrocarboxylates. Mass spectral analysis of glycollic acid thioanhydrocarboxylate (GATA) looks very complex and it has been suggested that either (GATA) may be decomposed during the removal of toluene at 40°C (during the purification technique, section 8.1.1) and therefore polymerised, or decomposed during storage.

A route to the preparation of dimethyl thioanhydrocarboxylate (DMTA) has been found involving the corresponding reaction between α - hydroxyisobutyric acid with thiophosgene (section 8.1.2). This reaction has been studied under conditions which have previously been used for preparation of anhydrosulphites and anhydrocarboxylates. However, there is

a need to make a more thorough investigation into the mode of preparation and purification of the thioanhydrocarboxylate. Pyridine could also be used as an accelerator for the reaction between the copper salt or ∝ - hydroxy acid with thiophosgene. The method for the use of pyridine has been described[48,60], in the preparation of anhydrocarboxylates of ∝ - hydroxy acid, although previous work[121,122] has reported that pyridine reacts with thiophosgene to form isothiocyanates.

The successful preparation of thioanhydrocarboxylates needs more investigation of preparation, purification and separation especially to minimise the amount of parent acid impurity, since any moisture present in the reacting vessel causes conversion of any thioanhydrocarboxylate back to the parent acid.

There is no available literature on thioanhydrocarboxylates of ∝ - hydroxy carboxylic acid. Recent work[123] has shown that thiophosgene reacts with 1 - amino cyclohexane carboxylic acid leading to the formation of unstable 4 - oxo - 2 - thioxo - 3 - oxa - 1 - azaspiro [4.5] decane (XXXXl) as shown in Equation (8. 3)



..... (8.3)

(XXXXl)

Thiophosgene (also named thiocarbonyl dichloride), has been known for many years, but its use in organic synthesis, till recently, has been limited to the preparation of a small group

of compounds. The carbon atom of thiophosgene has high electrophilicity so it reacts easily with compounds having a lone pair of electrons eg. nitrogen compounds[123] and alcohols.[124]

Attempts at synthesis met with two difficulties. In the first place, the reaction is much slower than those involving phosgene . Secondly, the products obtained contain impurities (eg. residual acid and chlorine containing species), although some success was obtained as evidenced by amine reaction. From these experiments and the limited amount of previous work[34] it seems that the thioanhydrocarboxylates are intermediate in physical properties between anhydrosulphites and anhydrocarboxylates. Whereas the former is a readily distilled liquid and the latter is a crystalline solid, thioanhydrocarboxylates seem to be viscous oils and not easily purified. More work was obviously needed for the successful preparation of these compounds but the time was considered as being more appropriately used to continue other lines of work.

CHAPTER 9

CONCLUSIONS AND SUGGESTIONS FOR FURTHER WORK

9.1 Conclusions

The work which is presented in this thesis is concerned with the preparation and purification of some cyclic derivatives of α - hydroxy carboxylic acids. In addition, the polymerisation and copolymerisation of these monomers in the presence of a range of initiators has been examined. Although the preparation and purification of such compounds (anhydrosulphites and anhydrocarboxylates) needs rigorous conditions in order to obtain pure monomers and careful handling to avoid contamination by moisture, ring-opening polymerisation of these compound provides a unique route to the synthesis of a wide range of poly - α - esters.

Pyridine and its derivatives have been used as initiators in the decomposition of the anhydrocarboxylate of α - hydroxyisobutyric acid (DMAC). Initiation of DMAC by this method provides a valuable method for ring-opening of the monomer and results in the formation of a crystalline poly - α - ester. The rate of polymerisation was found to be first-order in monomer and first-order in pyridine (although with deviation at high pyridine concentration). The rate of the decomposition unfortunately proceeds at a rate slower than would be needed for efficient copolymerisation with unsubstituted monomers, for example glycollic acid anhydrocarboxylate (GAAC) or glycollic acid anhydrosulphite (GAAS). However, the results in Table (4.1) show that pyridine initiation provides an extremely rapid method of DMAC decomposition compared with

other methods (eg. thermal and protonic decomposition) in spite of the presence of two sterically hindered methyl groups in the ring.

The polymers prepared via the pyridine initiated route were of relatively low molecular weight in spite of rigorous purification procedures for the solvents and the initiator. Adventitious traces of moisture, which may be present in the polymerisation system, limit the high molecular weight production by termination of the growing polymer chains. Other termination reactions that limit the molecular weight may be involved but were not examined here.

The decomposition of anhydrocarboxylates (glycollic acid anhydrocarboxylate, GAAC and α - hydroxyisobutyric acid anhydrocarboxylate, DMAC) and anhydrosulphite (glycollic acid anhydrosulphite GAAS) in the presence of lithium tertiary butoxide has been examined, in order to achieve a lower temperature ring-opening polymerisation and to obtain background information to enable potential biomedical copolymers to be formed. Lithium tertiary butoxide is successful in the decomposition of DMAC, GAAC and GAAS and the products were (i) Poly -α- ester and (ii) lithium metal salt, kinetic analysis showed that the reactions in general tend not to be first order overall, but possibly first-order in the initial stages. The deviation from first-order behaviour in the latter stages of the reaction may be due to heterogeneity. The similarities between Crowe's work[93] (lithium tertiary butoxide with disubstituted anhyrdosulphites) and the present work (anhydrocarboxylates and unsubstituted anhydrosulphite) with respect to the kinetic behaviour and the products produced suggests that the

same mechanism that Crowe applied to the anhydrosulphites could be applied to the anhydrocarboxylates. This mechanism involves the use of the alkoxide as a catalyst in the polymer producing reaction, for the breakdown of the anhydrocarboxylate ring and formation of a highly reactive intermediate together with regeneration of the alkoxide with release of carbon dioxide. This intermediate, which can be regarded as an α - lactone , reacts with any available nucleophile including parent acid, the initiator alkoxide and polymer chain ends.

Monomers containing a carboxyl functional group (tartronic acid anhydrosulphite, TAAS and tartronic acid anhydrocarboxylate TAAC) which were prepared from an α - hydroxy acid with two carboxyl groups(eg. tartronic acid) were synthesised successfully from a direct reaction between tartronic acid and reaction reagents (thionyl chloride and phosgene) rather than via the copper(11) salt. This is due to the fact that, firstly the thionyl chloride and phosgene reacts without difficulty with the hydroxyl group of the acid and secondly due to the difficulty with drying the copper (11) salt of tartronic acid. As far as anhydrocarboxylate synthesis is concerned, an improved procedure has been developed which involved the use of 1,4-dioxan as a solvent instead of ether in the novel synthesis of tartronic acid anhydrocarboxylate (TAAC). Tartronic acid anhydrocarboxylate (TAAC) was synthesised with higher purity than tartronic acid anhydrosulphite (TAAS), because TAAC is solid and the use of silver oxide was sufficient to remove the chlorine impurities whereas TAAS is a liquid which needs distillation at high temperature for the purification.

Thermal decomposition of the tartronic acid anhydro-

sulphite (TAAS) in the absence of added initiators has been studied in order to assess the feasibility of this reaction mechanism as a route to the poly- α - ester. Kinetic studies indicated that the decomposition of TAAS at all temperatures, was a first-order process with the evolution of sulphur dioxide leading to the polymer contaminated with by-products. Contamination is due to the susceptibility of the monomer to a secondary fragmentation process yielding sulphur dioxide, carbon monoxide and glyoxylic acid (Equation 6.9), which considerably reduced the yield of polytartronic acid produced. However, the mass spectral analysis of TAAS showed only a very small peak (M - 64) indicating unstable α - lactone, therefore, thermal decomposition of TAAS is not a satisfactory method to produce a reasonable yield of polytartronic acid since this process requires generation of the α -lactone. Another method of generating α - lactone species (ie. tertiary base initiation) was examined, to enable rapid but controlled polymerisation to be achieved at room temperature. The produced polymer (polytartronic acid) was hygroscopic and was difficult to characterise except by infra-red spectroscopy.

Thermal decomposition of tatronic acid anhydrocarboxylate (TAAC) was examined and the polymer (polytartronic acid) was obtained with reasonable molecular weight. However, when different initiators were examined with TAAC, the products were believed to be polymers with low molecular weight. In this study, 2,6 - Lutidine (higher nucleophilicity was more reactive with tartronic acid anhydrocarboxylate

(TAAC) than was pyridine, this shows that in the case of monosubstituted cyclic monomer (eg. TAAC), the basicity of the tertiary base is more important than steric hindrance. The reverse situation was found (chapter 3) in the case of the disubstituted anhydrocarboxylate (eg. dimethyl anhydrocarboxylate DMAC).

Copolymerisation of TAAS and TAAC with mono and disubstituted anhydrosulphite (mainly GAAS and HBAS) has been examined to enable copolymers containing functional groups to be formed, since these are of potential biomedical interest. The hygroscopic products from this copolymerisation were generally more characteristic of polytartronic acid than of the desired copolymers.

A number of polystyrene supported pyridine catalysts were examined as initiators for the decomposition of dimethyl anhydrosulphite (HBAS) and spiro-cyclohexyl anhydrosulphite (Chex AS) in order to assess the feasibility of using these catalysts to synthesise poly - α - ester at a controlled rate. Kinetic studies indicated that the decomposition of HBAS and Chex AS was first-order with respect to monomer and shows dependence on the amount of the catalyst present. Separation of the products (poly - α - esters) from this kind of polymerisation was easier than when using pyridine as initator in that the product from polystyrene supported pyridine catalyst is white and cleaner, while from pyridine initiation, the product was coloured and of low molecular weight.

The attempted synthesis of α - hydroxy isobutyric acid thio-anhydrocarboxylate (DMTA), glycollic acid thioanhydrocarboxylate (GATA) and lactobionic acid anhydrosulphite (LBAS) has been examined as these represent novel functional monomers.

The difficulty in preparing pure samples of thioanhydrocarboxylates is mainly due to the low reactivity of thiophosgene. The time required for thiophosgene to react with cupric glycollate and α - hydroxy isobutyric acid facilitates the formation of a number of side products. However, dimethyl thioanhydrocarboxylate (DMTA) was successfully synthesised from reaction between α - hydroxy isobutyric acid with thiophosgene.

The attempted synthesis of lactobionic acid anhydrosulphite (LBAS) from the silver salt of lactobionic acid with thionyl chloride demonstrated the advantage that for the α - hydroxy carboxylic acid with one carboxylic group and several hydroxyl groups (eg. lactobionic acid), the preparation of cyclic monomers is achieved more easily by using the silver salt of the parent α - hydroxy acid.

Characterisation of the products (poly - α - ester) from decomposition of cyclic derivatives of α - hydroxy carboxylic acid which have been examined in this thesis were mostly carried out by i.r. spectroscopy, x-ray and gel permeation chromatography. Nuclear magnetic reasonance spectroscopy is a useful method to complete the characterisation of the polymer structure, but unfortunately difficulty is encountered in the solubility of the products in the solvents which are commonly used in this technique. However, it would be useful if a suitable solvent could be found to solve this problem by using the FT NMR instrument which has now been made available in this department.

9.2 Suggestions for Further Work

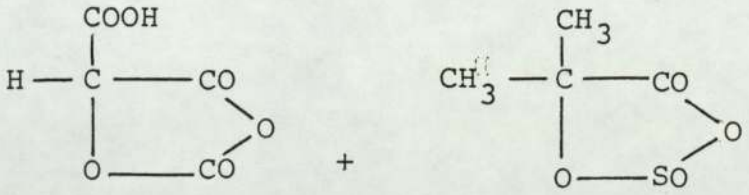
The work described in this thesis has established general areas. More detailed studies are necessary to exploit this field of ring-opening polymerisation. The most important single requirement is the use of n.m.r. to establish more completely the structures of the various monomers and polymers discussed in the thesis.

The aprotic base 2,6-Lutidine has been studied and was found to be a better initiator than pyridine when polymerisation was carried out with tartronic acid anhydrosulphite TAAS (the polymerisation was more controlled with a lower exotherm). Copolymerisation of tartronic acid and α - hydroxy isobutyric acid anhydrosulphites was also attempted and copolymers have been formed. These polymers have potential usefulness in the biomedical field. Optimum conditions for this type of copolymerisation can only be predicted on the basis of kinetic studies that are described here since these enable us to understand the mechanism of the reactions.

An alternative method to overcome the problem of the high reactivity of pyridine with anhydrosulphites in the copolymerisation with anhydrocarboxylate may be by using polystyrene supported pyridine catalyst which has proved to be less reactive than pyridine alone. This may be useful in the copolymerisation of anhydrosulphites with anhydrocarboxylates containing a functional group (eg TAAC).

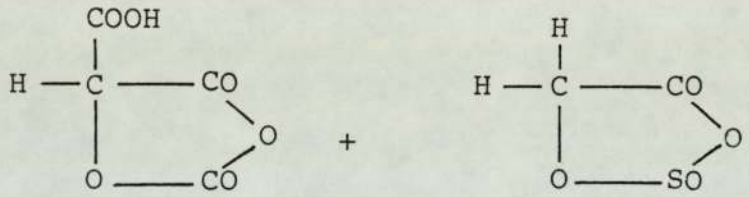
It has already been established that lithium tertiary butoxide is a good catalyst for the polymerisation of some cyclic monomers for example anhydrosulphites. It would be advantageous to study the effect of solvents in more detail.

These (or other) novel initiators may enable more equal copolymerisation rates to be achieved for monomer pairs such as



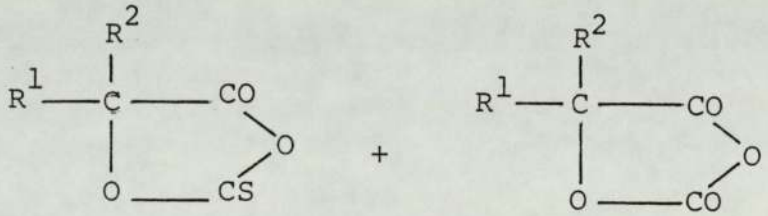
TAAC HBAS

and

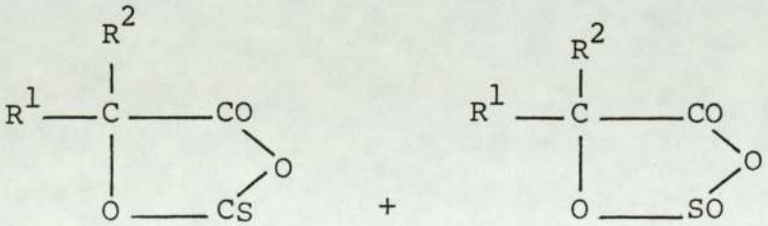


TAAC GAAS

whose copolymers are of considerable interest. For the same reason it would be valuable to examine the copolymerisation of thioanhydrocarboxylate and anhydrocarboxylate.



and thioanhydrocarboxylate and anhydrosulphite



since this may lead to more even rates of copolymerisation with different pairs of R^1/R^2 groups. The synthetic difficulty may prevent this from being achieved, however, further work must include more efficient purification and more complete characterisation of monomers and the polymerisation products.

The greatest potential value of the synthesis of thioanhydrocarboxylates lies in copolymerisation work. This would be especially true if it proved possible to copolymerise these rings with anhydrocarboxylates and thereby overcome the problems associated with the effect of substituents such as - COOH on ring reactivity.

Polystyrene supported catalyst has great advantage for copolymerisation of functional monomers (eg. tartronic acid anhydrosulphite and tartronic acid anhydrocarboxylate), but unfortunately arrived too late for use in this project. There are many aspects of their behaviour that are of interest, in particular the site of formation of polymer and its ability to diffuse in the gel network. Such catalyst will generally be relatively valuable and important and there would be more advantages to use this catalyst in the copolymerisation.

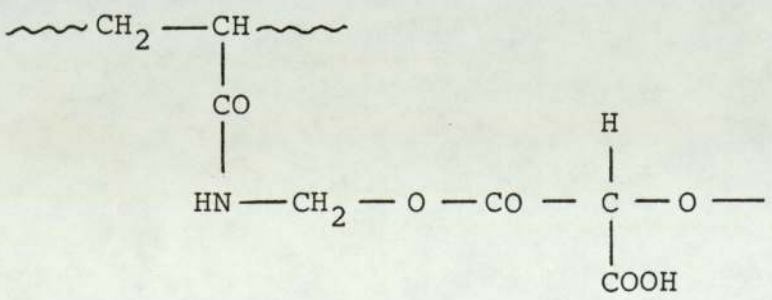
A list of ideas for further work would be more helpful with respect to the tartronic acid derivatives (ie. TAAS and TAAC), these are listed below:-

(1) A more suitable mode of polymerisation of TAAS and TAAC needs to be found by the use of more suitable initiators.

2) It would be valuable to investigate other methods of purification for TAAS and TAAC. The use of a chromatographic separation method seems to be more preferable since this might remove both chlorine and acid impurities.

(3) The gas evolution technique has provided a valuable indication of the thermal decomposition of TAAS. However, using initiators and solvents best suited to TAAS and TAAC polymerisation may interfere with gas evolution measurement (eg. basic initiators interfere with SO_2, low volatile solvents produce high initial pressure). It would be valuable to continue work using spectroscopic techniques, particularly infra-red and n.m.r. which has the advantage that much smaller quantities of reactants can be used than with gas evolution, and the concentration of all species present at any given time can be evaluated.

(4) The choice of suitable copolymer systems involving TAAS and TAAC is potentially valuable for producing biocompatible drug-carrying polymers. It is suggested that copolymerisation of TAAS or TAAC with N- methylol acrylamide - containing polymer may give the following copolymer.



It is hoped that the work presented herein will provide a system which is capable of many extensions in the various fields of biomedical polymers.

REFERENCES

NUMBER	AUTHOR (S)
1	Wurtz, A, Ann-Chim. Phys., 69, 330, 334, 1863.
2	Bischoff, C.A. and Walden,P.W., Ann., 279, 45, 1893.
3	Dall'Asta, G., Rubber Chem.and Tech.,47, 511, 1974.
4	Ivin,K.J.,Tapienis, G,and Rooncy, Polymer,21, 367, 1980.
5	Frisch, K.C., and Reegen, S.L. (Eds), "Ring-opening polymerisation", Marcel Dekker, 1969.
6	Frisch, K.C., "Cyclic Monomers", High Polymers Vol. XXVl.
7	Still, J.K.,Introduction to Polymer Chemistry, Wiley, 1962.
8	Odian, G.,Principles of Polymerisation. McGraw - Hill, 1970.
9	Dainton, F.S., and Ivin, K.J., Quart . Rev. (London), 12, 61, 1958.
10	Stark B.P., and Duke, A.J., "Extrusion Reactions", Pergamon, 1967.
11	Eliel, E.L.,stereochemistry of carbon compounds, McGraw - Hill, New York, 1962.
12	Pines, H., Huntsman. W.D., and Ipatutt, J.Amer. Chem. Soc., 75, 2315, 1953.
13	Hall, H.K.,and Schneider, A.K., J.Amer. Chem. Soc., 80, 6409, 1958.
14	Small, P.A., Trans. Farad. Soc., 51, 1717. 1955.
15	Mark, H., and Whitley, G.S. (Eds), "The collected papers of W.H.O. Carothers", Wiley (interscience), New York, 1940.
16	Borwell, F.G., and Knipe, A.C., J. Org.Chem., 35, 2956, 1970.
17	Leffler, J.E., and Zepp, R.G., J.Amer. Chem. Soc., 92, 3713, 1970.
18	Ballard, D.G.H., and Tighe, B.J., J.Chem.Soc., 702, 1967.
19	Tighe, B.J., Reprint from Chemistry and Industry, 1837, 1969.

NUMBER	AUTHOR (S)
20	Adam, W., and Rucktäschel, R., J.Amer. Chem. Soc., 93, 557, 1971.
21	Encyclopedia of Polymer Science and Technology, Vol. 11
22	British Pat. 1, 494, 781, 1977.
23	Blaise,E.E., and Marcilly, L., Bull. Soc. Chim. Fr,(3), 31, 308, 1904.
24	Fichter, F., and Beisswenger, A., Chem.Ber., 36, 1200, 1903.
25	Carothers, W.H., Dorough, G.L., and Van Natta, F.J., J.Amer. Chem. Soc., 54, 761, 1932.
26	Bischoff, C.A., and Walden, P.W., Ber., 36, 1200, 1903.
27	Bischoff, C.A., and Walden, P.W., Ber., 26, 262, 1893.
28	Bischoff, C.A., and Walden, P.W., Ber., 27, 71, 1894.
29	Delbig,H., Geiger, J., and Sander, M., Die Makromol. Chemie, 145, 123, 1971.
30	Cox, E.F., and Hostettler, F., U.S. Patent, 3, 021, 313, 1962.
31	Farthing, A.C., J. Chem. Soc., 3213, 1950.
32	Davies, W.H., J. Chem. Soc., 1357, 1951.
33	Ali, M.M., Ph.D. Thesis, University of Aston in Birmingham, 1975.
34	Prendergast, K.M., B.Sc. Project, University of Aston in Birmingham, 1972.
35	Kato, H., Higoshinura, T., and Okamura, S., Die Makromol Chemie, 9, 109, 1967.
36	Dewey et.al, R.S., J. Org. Chem., 36, 49, 1971.
37	Davies, A.C., and Levy, A.L., J.Chem. Soc., 24, 2419, 1951.
38	Bradbury, J.H., and Leeder, J.D., Textile Research J., 30, 118, 1960.
39	Billimaria, J.D.and Cook A.H., J.Chem. Soc., 2323, 1949.
40	Cook, A.H., and Levy, A.L., J. Chem. Soc., 651, 1950.
41	Ali, M., Roy, S., and Tighe, B.J., J.Appl. Biotecnhol., 27, 696, 1977.

NUMBER	AUTHOR(S)
42	Kopple,K.D., J. Amer. Chem. Soc. 79, 662, 1957.
43	Katchalski,E., and Sela, M., Advan. Protein Chem., 13, 249, 1958.
44	Leuchs, H. Chemie. Ber., 39, 857, 1906.
45	Bamford, C.H., and Block, D.G.H., J.Chem. Soc., 2057, 1961.
46	Woodward,R.B., and Schraw, C.H., J.Amer. Chem. Soc., 69, 1551, 1947.
47	Moore, T.A., Dice, J.H., Nicolaides, E.D., Westland, R.D., and Wittle, E.L., J. Amer. Chem. Soc., 76, 2884, 1954.
48	Ballard, D.G.H., and Bamford, C.H., Proc. Roy. Soc., A223, 495, 1954.
49	Idelson, M., and Blout, E.R., J.Amer. Chem. Soc. 79, 3948, 1957.
50	Blout, E.R., Karlson, R.H., Doty, P., and Hargitay, B., J. Amer. Chem. Soc., 76, 4492, 1954.
51	Idelson, M., and Blout, E.R. , J. Amer. Chem. Soc., 80, 2387, 1958.
52	Ballard, D.G.H., Bamford, C.H., and Weymouth, F.J., Proc. Roy. Soc., 227, 155, 1955.
53	Noma, K., and Tsuchida, T., Kobunshi Kagaku, 6, 109, 1949.
54	Sela, M. and Berger, A., J. Amer. Chem. Soc., 75, 6350, 1953.
55	Sela, M. and Berger, A., J. Amer. Chem. Soc., 77 1893, 1955.
56	Fessler, J.H. and Ogston, A.G., Trans. Faraday Soc., 47, 667, 1951.
57	Pope, M.T., Weakley, T.J., and Williams, R.J.P., J. Chem. Soc., 3442, 1959.
58	Lundberg, R.D., and Doty, P., J. Amer. Chem. Soc., 79, 3961, 1957.
59	Davies, W.H.,J. Chem. Soc. 1357, 1951.
60	Tighe, B.J.,Ph.D. Thesis, University of Aston in Birmingham, 1966.
61	Ballard, D.G.H., and Tighe, B.J., J. Chem.Soc., (B) 976, 1967.

NUMBER	AUTHOR (S)
62	Thomas, M.D., and Tighe, B.J., J. Chem. Soc., B 1039, 1970.
63	Blackbourn, G.P., and Tighe, B.J., J. Poly. Sci., 8, 3591, 1970.
64	Blackbourn, G.P., and Tighe, B.J., J. Chem. Soc. (B), 1384, 1971.
65	Pedly, D.G., and Tighe, B.J., J. Poly. Sci. (Polym. Chem. Ed.), 11, 779, 1973.
66	Blackbourn, G.P.,and Tighe, B.J., J. Chem. Soc. (C), 257, 1971.
67	Blackbourn, G.P., and Tighe., B.J., J. Poly. Sci. 10, 295, 1972.
68	Beecham Group Ltd., Belg. Patent, 819436, 1975, CA., 87, 201318, 1977.
69	Smith, I.J., and Tighe, B.J., J. Poly. Sci., 14, 949, 1976.
70	Smith, I.J., and Tighe, B.J., J. Poly. Sci., 14, 2293, 1976.
71	Evans, B.W., Fenn, D.J. and Tighe, B.J., J.Chem. Soc. (B), 1049, 1970.
72	Fenn, D.J., Thomas, M.D., and Tighe, B.J., J. Chem. Soc. (B), 1045, 1970.
73	Crowe, A.J. and Tighe, B.J., Chem.and Ind., 170, 1969.
74	Evans, B.W., Tighe, B.J., and Wittingham, A., Br. Poly. J., 233, 1970.
75	Smith, I.J., and Tighe, B.J., Chem. and Ind., 695, 1973.
76	Smith, I.J., and Tighe, B.J., Br. Poly. J., 349, 1975.
77	Rose, J.B. and Warren, C.K., J. Chem. Soc. (London), 791, 1967.
78	Alderson, T., U.S.P. No. 2, 811, 511, 1957.
79	Chapman, O.L, Wojtkowski, P.W., Adam, W., Rodriguez, O., and Rucktaschel, R., J. Amer. Chem. Soc., 94, 1365, 1972.
80	Swarc, M., Fortshr, Hoch polym. Forch., 1, 4, 1968.
81	Bamford, C.H., and Block, D.G.H., J. Chem. Soc., 4989, 1961.

NUMBER	AUTHOR(S)
82	Szwarc, M., Advan, Polym. Sci., 4, 1 - 65, 1965.
83	Sekiguchi, H., and Froyer, C.R., Acad. Sci. Paris, C 279, 623, 1974.
84	Roth, M., and Mühlhausen, D., Angew. Chem. 88, 338, 1976.
85	Wichterle, D., Sebenda, J., and Kradicek, J., Advan. Polymer, 2, 578, 1961.
86	Bamford, C.H., and Block, H., Polyamino acids, polypeptides and proteins, (M.A. Stahmann, ed.) Univ, Wisc. Press, Madison, 65, 1962.
87	Inoue, S., Tsubaki, K., and Tsuruta, T., Makromol. Chem., 125, 170, 1969.
88	Inoue, S., Tsubaki, K., and Tsuruta. T., Polymer Lett., 6, 733, 1968.
89	Kosolsumollamps, N., Ph. D. Thesis, University of Aston in Birmingham, 1976.
90	Smith, I.J., Ph. D. Thesis, University of Aston in Birmingham, 1972.
91	Penny. W.A. Ph.D. Thesis, University of Aston in Birmingham, 1980
92	Smith, I.J., and Tighe, B.J., Makromol. Chem., 182, 313, 1981.
93	Crowe, A.J., Ph. D. Thesis, University of Aston in Birmingham, 1975.
94	Crowe, A.J., and Tighe, B.J., Br. Polym. J., 6, 79, 1974.
95	Eavns, J.M., RAPRA Bulletin, 334, 1972.
96	Ingrams, G., Mikrochim. Acta. 877, 1956.
97	Vogel, A.I., Practical Organic Chemistry, Longmans, London, 1964.
98	Weissberger (Ed.), "Technique of Organic Chemistry" vol. VII, Second Edition, Interscience, New York, 1955.
99	Gerrard, W., and Howe, B.K., J. Chem. Soc., 5105, 1955.

NUMBER	AUTHOR(S)
100	Gerrard, W., and Schild, F., Chem and Ind., 1232, 1954.
101	Blackbourn, G.P., Ph.D. Thesis, University of Aston in Birmingham, 1970.
102	Samitou, Y.Y., and Aminova, R.M., J. Struc. Chem., 5, 497, 1963.
103	Brown, H.C., and Mihm, X.R., J. Amer. Chem. 77, 1723, 1955.
104	Katritzky, A.R., and Lagowski, J.M., "Principles of Heterocyclic Chemistry", Metheun, 1967.
105	Sarguroh, A., M.Sc. Thesis, University of Aston in Birmingham, 1977.
106	Leffer, T.E., and Grunwald, E., "Rates and Equilbria of Organic Reactions", John Wiley and Sons, 1963.
107	Wieland, T., Angew Chem., 66, 507, 1954.
108	Wieland, T., Angew Chem., 63, 7, 1951.
109	Ballard, D.G.H., and Bamford, C.H., J. Chem. Soc., 381, 1956.
110	Gold, V., and Jefferson, E.G., J. Chem. Soc., 1413, 1409, 1953.
111	Sekiguchi, H., and Doussin, J.F., Biopolymers, 15, 1431, 1976.
112	Bloute, E.R., and Karlson, R.H., J. Amer. Chem. Soc., 78, 941, 1956.
113	Lycan, W.H., and Adams, R., J. Amer. Chem. Soc., 51, 625, 1929.
114	Tighe, B.J., in 'Macromolecular Chemistry', edr.Jenkins, A.D., and Kennedy, J.F., 1980
115	Donaruma, L.G., and Vogl,O., EDS., Polymeric Drugs, Academic Press, New York, 1978.
116	Ratner, B.D., and Hoffman, A.S.'Hydrogels for Medical and Related Applications, P 1-36 (American Chemical Society), 1976.

NUMBER	AUTHOR(S)
117	Hodge, P.,and Sherrington, D.C., Eds., "Polymer-Supported Reactions in Organic Synthesis", 1980 London, W.J. Wiley.
118	Greig, J.A., and Sherrington, Polymer, 19, 163, 1978.
119	Sherrington, D.C., Craig, D.J., Dalgleish,J., Domin,G., Tayloe, J., and Meehan, G.C., Eur. Polym. J., 13, 73, 1977.
120	Frechet, J.M.J., Farrall, M.J, and Nuyens, L.J., J. Macromol Sci. A, 11, 507, 1977.
121	Hull, R., J. Chem. Soc. [C], 1777, 1968.
122	Boyle, F.T. and Hull, R., J. Chem. Soc. Perkin Trans., 1, 1541, 1974.
123	Cook, C.H., Cho, Y.S. and Jew, S.S., J. Pharmaceutical Soc. of korea, 16, 85, 1972, C.A. 80, 70741, 1974.
124	Martine, D., Weise, A., and Niclas, H.J., Angew. Chem. Internal. Edit., 6, 318, 1967.
125	Roy, S., Ph.D. Thesis, University of Aston in Birmingham, 1978.