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ZWITTERION POLYMERIZATION OF 2-METHYL-2-OXAZOLINE AND ACRYLIC ACID

BY

PATHIRAJA A. GUNATILLAKE

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosopy, The City University of New York.

1983

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosopy.

9/28/83
date

George Odian
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9/28/83
date

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Dr. H. HAUBENSTOCK H. Haubenstock

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Supervisory Committee

The City University of New York

Abstract

ZWITTERION POLYMERIZATION OF 2-METHYL-2-OXAZOLINE AND ACRYLIC ACID

By

Pathiraja A Gunatillake

Adviser: Professor George Odian

The zwitterion polymerization of 2-methyl-2-oxazoline(MeOXO) and acrylic acid (AA) has been investigated in bulk and solution (DMF and acetonitrile) at 60-70°C. Variation of reaction conditions such as temperature, methods of monomer addition, high vacuum conditions to avoid adventitious terminating agents, solvents , and addition of a nucleophile to the reaction system resulted in copolymers having number average molecular weights in the range 590-2760 as determined by vapor pressure osmometry.Three stage polymerization showed that the MeOXO-AA monomer system does not behave as one with living characteristics. The copolymer composition was estabilished as 1:1 (MeOXO:AA) by proton NMR.Proton and ^{13}C NMR spectroscopy identified the repeating unit as $-CH_2CH_2N(COCH_3)CH_2CH_2COO-$ and the end groups as olefinic($CH_2=CHCOO-$), carboxyl(-COOH) and acetamido ($-NHCOCH_3$). Infrared spectroscopy supports the NMR results. Hydrolysis experiments corroborated both the copolymer composition and identity of the end groups. N-(2-hydroxyethyl)-β-alanine(from the repeating unit) was isolated from the hydrolysis products of the copolymer.Presence of

acrylic acid (from the olefinic end group) and acetic acid(from the repeating unit) among hydrolysis products was confirmed by GC and analytical HPLC. Presence of ethanolamine (from the acetamido end group) was confirmed by isolating it as the dibenzoyl derivative. High performance liquid chromatography showed that the copolymer product consists of different-sized molecules and not all molecules have the same two end groups. Some molecules had olefinic and carboxyl end groups and the others olefinic and acetamido end groups.A mechanism is proposed to describe the MeOXO-AA polymerization.MeOXO and AA forms a genetic zwitterion which is responsible for initiation . Polymer growth involves various-sized zwitterions reacting with each other and with the genetic zwitterion by a ring opening attack of carboxylate anion on the quaternery MeOXO ring. Termination occurs by reaction of growing zwitterions both with acrylic acid and with a quaternized MeOXO-acrylate salt(formed by proton transfer between MeOXO-AA). Direct NMR analysis of the polymerizing MeOXO-AA system gave evidence for the genetic zwitterion and early termination of growing zwitterions by reaction with quaternized MeOXO-acrylate salt.

ACKNOWLEDGEMENT

I wish to express my sincere gratitude to Dr. George Odian for his guidance and encouragement in this work.

I like to thank Dr. Fred Naider for his valuble suggestions , Dr. N.L.Yang, Dr. Howard Haubedstock and Dr. A.E.Woodward for their help in my understanding of polymer science.

I am grateful to my wife, Chandra for her support in many ways and encouragement in this work. Help given by Miss. Margaret Coughlan is greatly appreciated.

I greatfully acknowledge financial support of this work by grants from the Dow Chemicla Co, National Science Foundation (DMR-8105865) and The City University of New York (PSC-CUNY 10-13140, 11-13350, 12-13685) as well as teaching appoinments from The College of Staten Island

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1.0 INTRODUCTION

Zwitterion polymerization is a recently discovered polymerization reaction which occurs spontaneously between nucleophilic (N) and electrophilic (E) monomers. Saegusa and coworkers (1-9) have reported a large number of pairs of nucleophilic and electrophilic monomers undergoing such polymerization to yield interesting polymer structures.These polymer structures contain a variety of functional groups as part of the polymer chain and pendant to the polymer chain. Polymers containing functional groups such as phosphonite , phosphate, carboxylate , amide , carbonyl, sulfonate and sulfonamide have been reported.

The N monomers studied include cyclic imino ethers, cyclic amines, cyclic phosphite and phosphonite, and imines. E monomers include β-propiolactone, acrylic acid and acrylamide, succinic anhydride and a sulfolactone (sultone) . Table 1 lists some of the specific monomers that Saegusa and coworkers studied. Saegusa has proposed the following general mechanism to explain the zwitterion polymerization of N and E monomers. Initially, the reaction of nucleophilic and electrophilic monomers forms an intermediate zwitterion which is referred to as the genetic zwitterion (I).

Initiation $\quad N + E \longrightarrow {}^{+}NE^{-}$ (I) $\quad (1)$

The genetic zwitterion is responsible for initiation as well as propagation. Two genetic zwitterions react to produce the first propagating species (II), which continues to grow by successive reactions with the genetic zwitterion.

Propagation

$$^{+}NE^{-} + {}^{+}NE^{-} \longrightarrow \underset{(IIa)}{^{+}NENE^{-}} \qquad (2)$$

$$\underset{(IIb)}{^{+}NE\text{-}(NE)_{\overline{n}}NE^{-}} + {}^{+}NE^{-} \longrightarrow \underset{(IIc)}{^{+}NE\text{-}(NE)_{n+1}NE^{-}} \qquad (3)$$

The propagating species which are larger than (I) are referred to as macrozwitterions. Polymer growth occurs not only by the reaction of macrozwitterion with genetic zwitterion but also by the reaction of two macrozwitterions.

$$^{+}NE\text{-}(NE)_{\overline{n}}NE^{-} + {}^{+}NE\text{-}(NE)_{\overline{m}}NE^{-} \longrightarrow {}^{+}NE\text{-}(NE)_{m+n}NE^{-} \qquad (4)$$

It is of interest to explore this new type of polymerization reaction as a means of synthesizing interesting polymer structures. However, this method has to-date been unsuccessful in generally synthesizing copolymers with high enough molecular weights for any practical utility. Saegusa and coworkers have mainly concentrated on investigating various possible N and E monomer combinations undergoing zwitterion polymerization. The experimental evidence provided is insufficient to understand the detailed rection mechanism and the copolymer structure.

No mention has been made about possible mode(s) of termination that limit the copolymer molecular weight.

We have investigated the zwitterion polymerization of 2-methyl-2-oxazoline with acrylic acid , 2-oxazoline with acrylic acid and 2-oxazoline with β-propiolactone with the following objectives.

a). To investigate the possibilities of synthesizing high molecular weight copolymers by considering reaction variables that can be used to overcome premature termination.

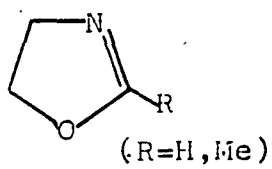
b). To illucidate the mechanism of zwitterion polymerization with emphasis on mode(s) of termination through characterization of copolymer.

2.0 BACKGROUND

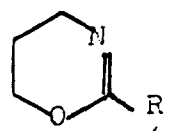
In 1972, Saegusa and coworkers (10) reported the first zwitterion copolymerization reaction between 2-oxazoline (N monomer) and β-propiolactone which proceed without the need of a catalyst or any added initiator to yield an alternating copolymer. Since then in more than two dozen publications, they have reported a large number of N and E monomer pairs undergoing zwitterion polymerization and some of the specific monomers studied are listed in Table I.

Table I

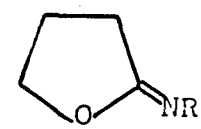
Nucleophilic Monomers (N)

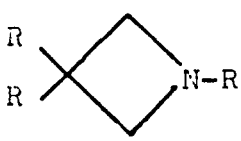


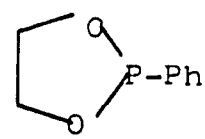
(R=H,Me)



(R=H,Ph)

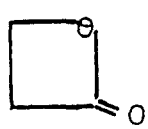


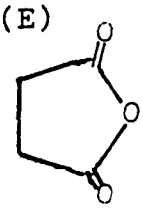


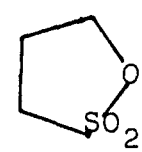


Ph-CH=NPh

Electrophilic Monomers (E)







CH_2=CHCOOH

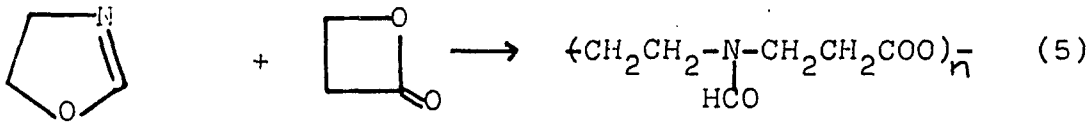
CH_2=CHCONH$_2$

CH_2=CHCOOCH$_2$CH$_2$OH

CH_2=CHSO$_2$NH$_2$

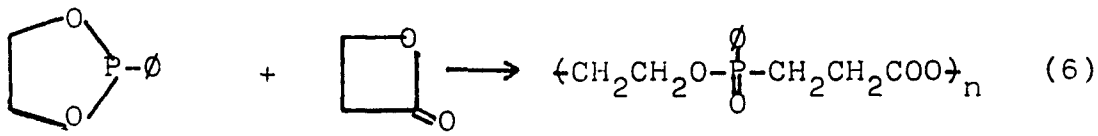
The scope of zwitterion polymerization can be seen by considering some of the systems which have been studied.

1. 2-Oxazoline (N) and β-propiolactone(E) or acrylic acid



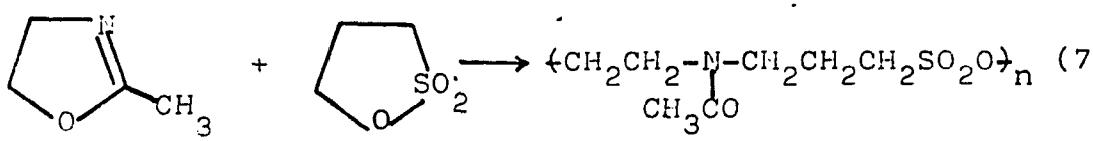
(5)

2. Ethylene phenylphosphonite (N) and acrylic acid or β-propiolactone(E)



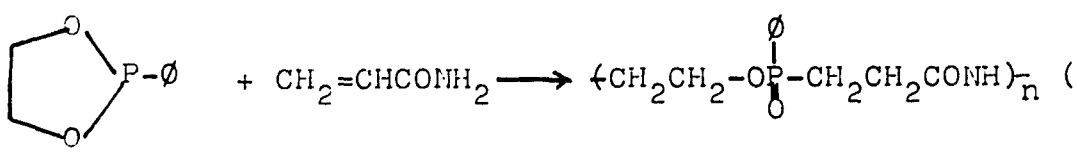
(6)

3. 2-Methyl-2-oxazoline (N) and 3-hydroxy-1-propane sulfonic acid sultone (E)



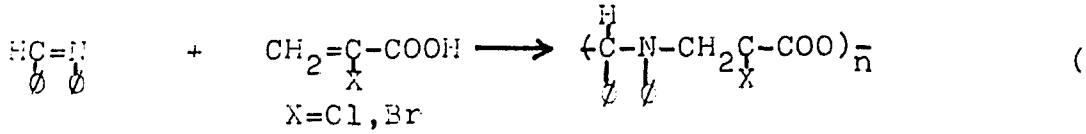
(7)

4. Ethylene phenylphosphonite (N) and acrylamide(E)



(8)

5. N-Benzylidine aniline (N) and α-chloroacrylic acid or α-bromoacrylic acid (E)



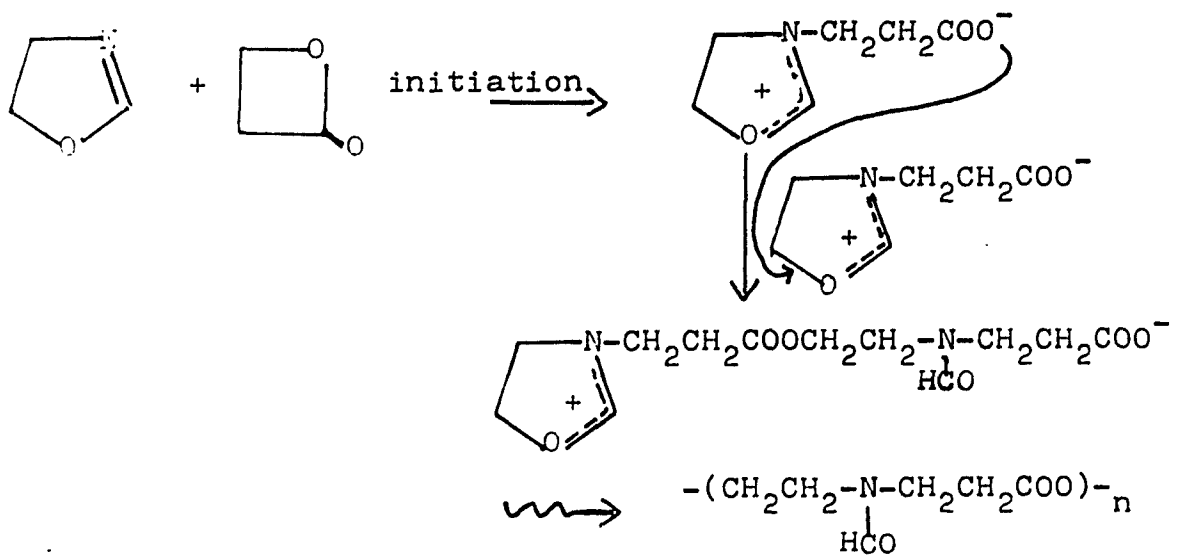
X=Cl,Br

(9)

Although over 25 pairs of monomers which undergo zwitterion polymerization have been reported , there is a general lack of understanding of the reaction mechanism that leads to early termination of copolymer chains.With no exceptions the basic experimental approach used by Saegusa et al involved the IR , NMR spectroscopic analysis , alkaline hydrolysis and elemental analysis of copolymer.It is appropriate to briefly discuss their experimental approach on a selected monomer pair , namely the OXO-BPL system which is the only system that has been studied in greater detail.

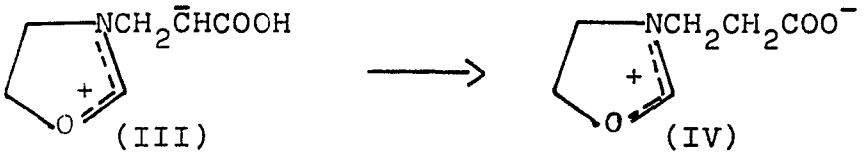
2.1 Copolymerization of 2-oxazoline with β-propiolactone

Based on the results of IR, NMR, elemental analysis and alkaline hydrolysis , the following mechanism has been proposed to explain the polymerization reaction.



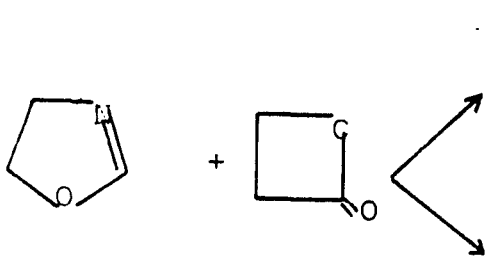
Interestingly when acrylic acid is used in place of

β-propiolactone the same product is obtained because the initially formed anion (III) undergoes proton transfer to yield the same anion (IV) as does β-propiolactone.



(10)

The amount of each monomer in the copolymer was determined by elemental analysis and H-NMR data. The proton NMR spectrum of a mixture of authentic samples of N-(2-Hydroxyethyl)-β-alanine and formic acid was compared with that of the hydrolysis products mixture.The similarity between these two spectra was taken to conclude the presence of N-(2-hydroxyethyl)-β-alanine and formic acid as hydrolysis products expected for the amide ester structure of the copolymer (V).The amide ether structure (VI) would have resulted different hydrolysis products (eq.14) other than (VII) and formic acid.



$$-(CH_2CH_2-\underset{\underset{HCO}{|}}{N}-CH_2CH_2COO)_n \qquad (11)$$

(V)

$$-(CH_2CH_2-\underset{\underset{HCO}{|}}{N}-COCH_2CH_2-O-)_n \qquad (12)$$

(VI)

$$V \xrightarrow{^-OH} HOCH_2CH_2NHCH_2CH_2COOH + HCOOH \quad (13)$$

(VII)

$$VI \xrightarrow{^-OH} H_2NCH_2CH_2OCH_2CH_2COOH + HCOOH \quad (14)$$

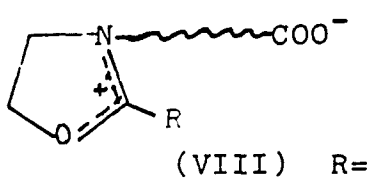
Similarly the presence of any random or block structure in the copolymer would have resulted in products other than (VII) and formic acid.

The results of the hydrolysis experiments are quantitatively inconclusive since no attempt was made to isolate any of the hydrolysis products.Although these results may suggest the possibility of a backbone structure V for the copolymer no mention can be made about the nature of the end groups which would have resulted different hydrolysis products . Even the proton NMR and IR spectroscopic data have not been discussed in sufficient details to understand the nature of the end groups.

The molecular weight of the OXO-BPL copolymer prepared in acetonitrile at 25°C has been reported to be 3500 (10,15) . The OXO-BPL system showed the characteristics of a living polymer system ; a second charge of the two monomers underwent complete polymerization and the molecular weight increased.However, the increased MW was only 4000.The molecular weight was observed to increase with the reaction temperature although the highest molecular weight observed was only 4100.

There was not sufficient data to indicate the effect of solvent on copolymerization reaction.Except for a very few monomer systems the molecular weights of the copolymers are uniformly very low (1000-4000). The highest molecular weight obtained was 13,500 for the 2-oxazoline acrylic acid system when the polymerization was done at 50-60°C in acetonitrile.However, the molecular weight was only 3710 when the polymerization was done at 50°C (14).

Although insufficient data are available to allow an understanding of the relationship between structure and polymerization behavior, it appears that the copolymer will deviate from a perfectly alternating structure when the nucleophilic and electrophilic reactivities of the comonomers are not balanced . 2-Oxazoline and β-propiolactone yield an alternating copolymer but when 2-methyl -2-oxazoline and 2-phenyl-2-oxazoline are reacted with BPL the copolymer contains 78% and 88% BPL respectively.The presence of the methyl or phenyl group stabilizes the cyclic imino ether oxonium ion (VIII) and decreases its reactivity towards the carbonyl end of another zwitterion.

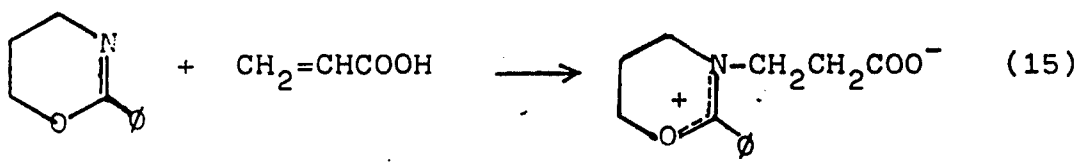


(VIII) $R=CH_3$, Ø

By default , the carboxylate anion initiates the homopolymerization of BPL.

With acrylic acid as the electrophilic monomer instead of BPL , even 2-methyl-2-oxazoline 2-phenyl-2-oxazoline as well as the unsubstituted 2-oxazoline , yield alternating copolymers as acrylic acid is not reactive toward anionic homopropagation.

There is no direct experimental evidence to show the formation of genetic zwitterions during the copolymerization reaction.However, in the copolymerization of 2-phenyl-5,6-dihydro-4H-1,3-oxazine (14) with acrylic acid a zwitterion intermediate (IX) has been isolated at low temperature (0°C).

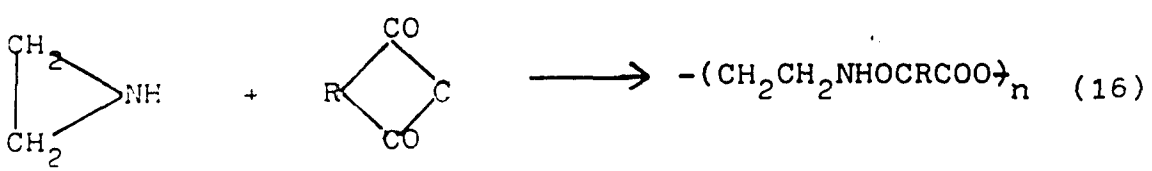


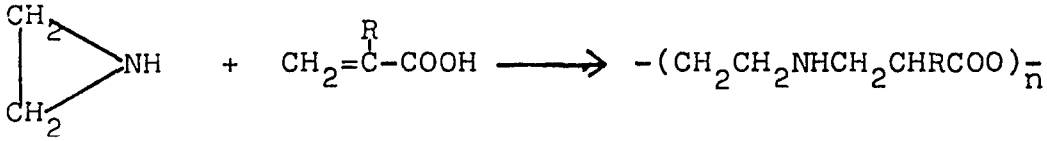
(IX)

The polymerization of the isolated zwitterion(IX) produced a copolymer having only a molecular weight of 800.

2.2 RELATED STUDIES

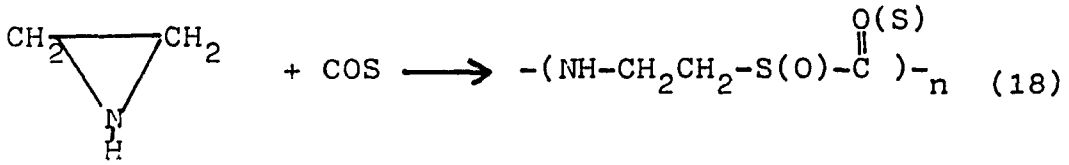
Aside from Saegusa's work , there are several other studies on zwitterion polymerization. Takashi(16,17) noted that ethylenimine undergoes zwitterion polymerization with dicarboxylic anhydrides and , unsaturated carboxylic acids to give very low molecular weight copolymers.





(17)

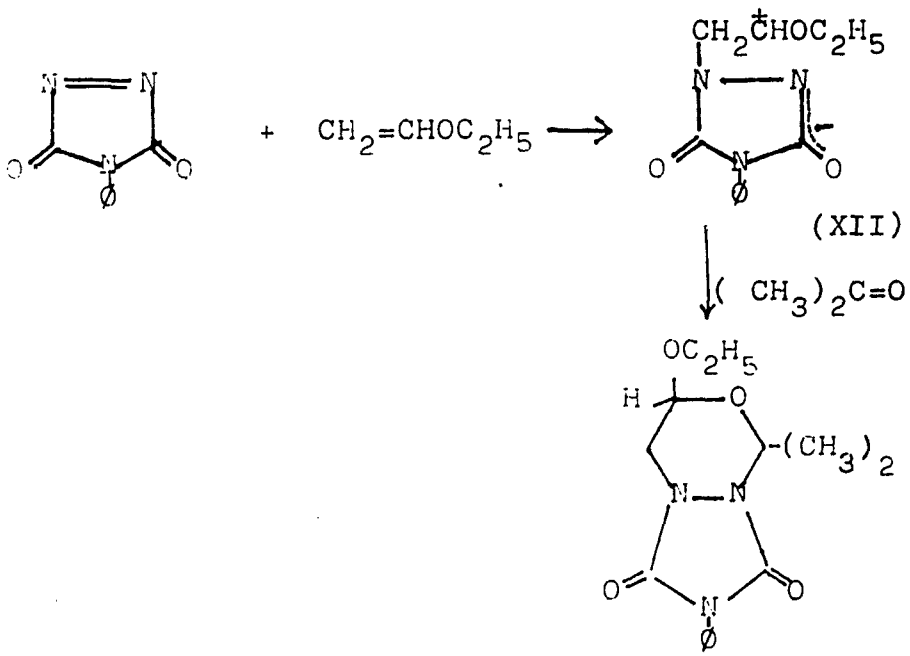
Several reported polymerizations which involve the zwitterion mechanism predate Saegusa's earliest reference.. including the spontaneous copolymerizations of ethylenimines (X) with carbonyl sulfide (XI) (18) and β-lactones (19) and 4-phenyl -1,2,4,-triazoline-3,5-dione with vinyl ethers and vinyl carbamate (20,21,22).



(18)

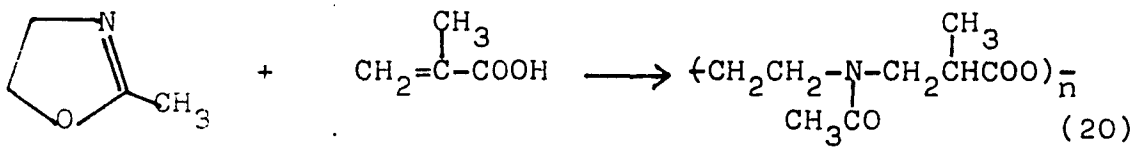
(X) (XI)

All of these systems gave low MW products . The papers by Butler and coworkers are of significance in that the existance of the zwitterion intermediate (XII) was estabilished by trapping with an aliphatic ketone.



(19)

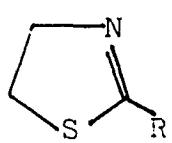
Balakrishnan and Periyasamy (13,23) have reported the zwitterion polymerization of 2-methyl-2-oxazoline with methacrylic acid and α-bromoacrylic acid , and a shiff base , N-benzylidine aniline with α-chloro and α-bromoacrylic acids(eq.9).



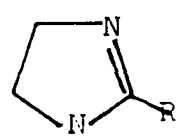
(20)

The copolymers are characterized by H-NMR and IR spectroscopy.On the basis of kinetic studies a zwitterion type mechanism similar to the Saegusa's mechanism have been proposed.

Tomalia and coworkers (24,25) studied the polymerization of acrylic acid with 2-alkyl -2-oxazolines, 2-thiazolines (XIII) and 2-imidazolines (XIV).

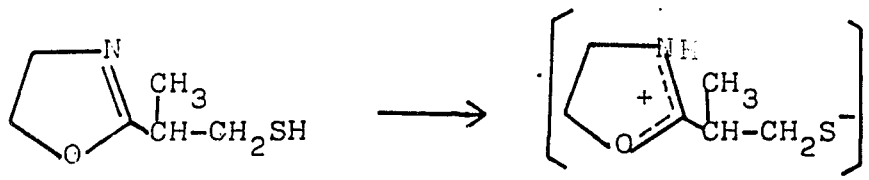


(XIII)

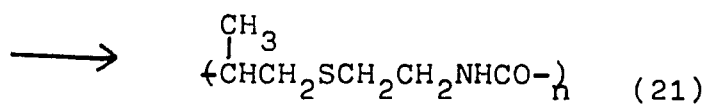


(XIV)

The three heterocyclics behave similarly. The polymerization of 2-(1-mercaptoisopropyl)-2-oxazoline(XV) reported by Tomalia and coworkers probably proceeds by the zwitterion intermediate XVI (formed by proton transfer from sulfur to nitrogen)



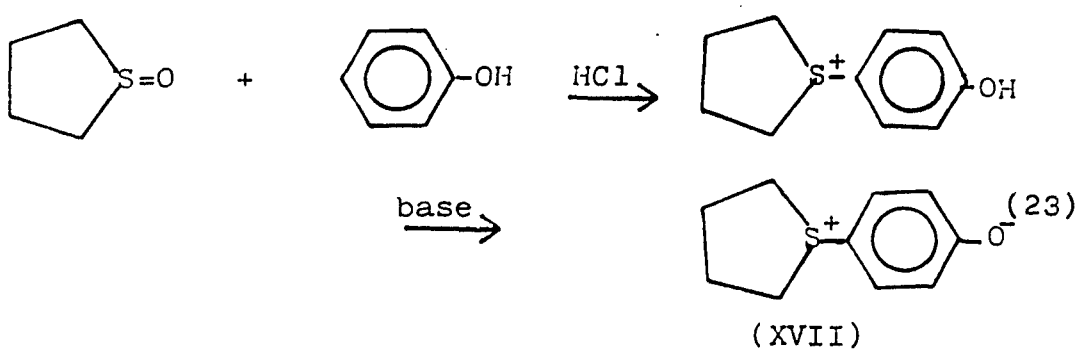
(XV) (XVI)



(21)

with the sulfide nucleophile attacking the oxazolinium ion at the C-O bond. The polymer molecular weights obtained are not high.(XV is formed by the radical addition of H_2S to 2-isopropenyl -2-oxazoline). The polymer molecular weight obtained by Tomalia in the various systems were not high. The products were not sufficiently characterized to identify the end groups and understand the reasons why high molecular weights were not obtained.

Schmidt and coworkers (26,27) synthesized and isolated cyclic sulfonium phenolate zwitterion XVI from the reaction of phenol with tetrahydro-thiophene-1-oxide by treatment with HCl followed by base.

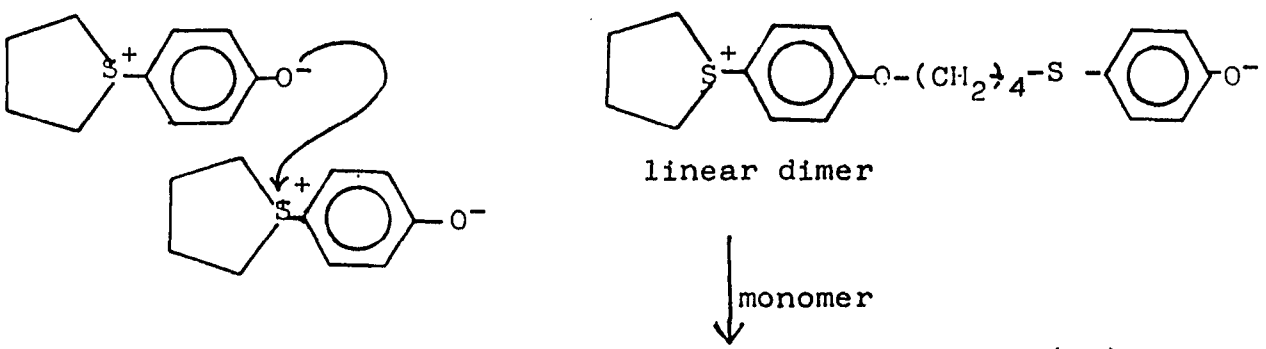


(XVII)

The preformed zwitterion XVII which was isolated as a

crystalline hydrate undergoes spontaneous polymerization upon removal of water at temperatures of 135-170°C. Molecular weights as high as 46,000 have been observed in the presence of a nucleophile such as NaOMe added at the beginning of the polymerization.Gel permeation chromatography coupled with mass spectroscopy showed the presence of about 5% each of cyclic dimer and trimer. Although this work has gone unnoticed by all other workers in the field it can be considered as the most significant work in zwitterion polymerization.

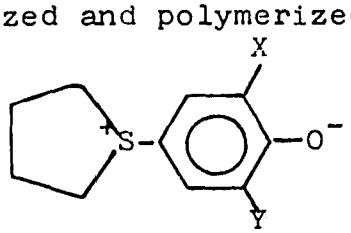
The mechanism involves displacement of sulfonium moity by a nucleophilic anion.



(23)

After the first initiation reaction, an active propagating species is produced which could grow from either or both ends of the chain until termination occurs.

Several aryl sulfonium zwitterions having substituents such as CH_3 and Cl on the aromatic ring have been synthesized and polymerized.



XVII; X=H, Y=CH_3
XIX ; X=CH_3,Y=CH_3
XX ; X=Y=Cl

The chlorinated zwitterion species (XX) are markedly more stable to polymerization than the unchlorinated analog (XVIII) and requires considerably high temperatures ($\simeq 170^{o}C$) . The low reactivity is considered to be as a result of the presence of electron withdrawing chlorine ortho to phenoxide group which causes a decrease in nucleophilicity . Addition of a nucleophile such as $NaOCH_3$ caused the polymerization to occur at temperatures below the polymerization temperature of pure XX and resulted in high molecular weight copolymers ($\bar{M}_n$ = 46,000).

The importance of zwitterion polymerization as a new method to synthesize a variety of new types of polymeric structures can be seen when considering the wide variety of monomer pairs reported in the literature. However, the molecular weights of polymers obtained are low in almost all the cases and poorley characterized as to chemical structure.The proposed reaction mechanism does not explain why only low molecular weight copolymers are obtained.

We have investigated the zwitterion polymerization of 2-methyl-2-oxazoline with acrylic acid , 2-oxazoline with β-propiolactone and acrylic acid with the objective of understanding the mechanism(s) that limit molecular weight and obtain high molecular weights in zwitterion polymerization.The choice of these monomer pairs was made because they are among the best characterized by Saegusa.

Except 2-oxazoline the other monomers are readily available and, in addition, the second system is that which gave the highest molecular weight in Saegusa's work.

Our research efforts were focussed on the following considerations.

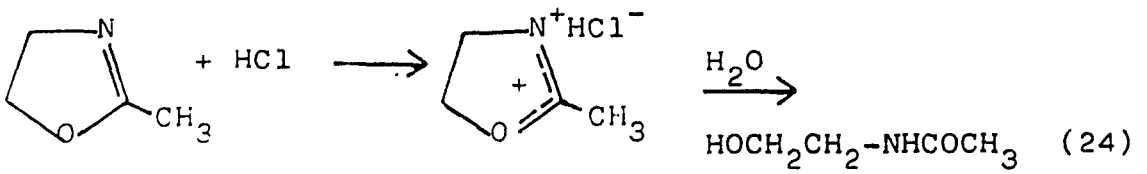
1). How does termination occur? How important are cyclization , reactions other than initial zwitterion formation between the monomers, intramolecular terminations and intermolecular terminations with adventitious species.

2). What reaction variables can be used to overcome premature termination and achieve high molecular weights.

3.0 PROPERTIES AND REACTIONS OF 2-OXAZOLINES

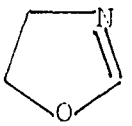
2-Oxazoline and 2-methyl-2-oxazoline are colorless liquids , miscible with water , and have a characteristic pyridine like odour(28-30). Physical properties and spectral data are summarized in Table II and III respectively.

2-Oxazolines are imino ether type compounds and nearly all of their reactions are attributable to this structure. They are weak bases (pK_a of MeOXO=5.5) and forms salts with dilute aqueous acids. For example, MeOXO reacts with dilute HCl to form a salt which on boiling with water gives N-acetyl ethanol amine(eq. 24).



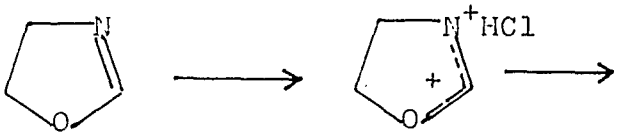
(24)

Although 2-methyl-2-oxazoline is stable to boiling water 2-oxazoline hydrolyzes to give β-hydroxyethyl formamide (31)



$$\xrightarrow[\Delta]{H_2O} \quad HOCH_2CH_2NHCHO \qquad (25)$$

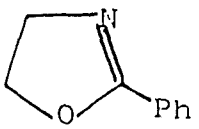
On the other hand 2-oxazoline forms an unstable hydrochloride salt which spontaneously hydrolyzes to N-β-chloroethyl formamide (29).



$$\longrightarrow ClCH_2CH_2NHCHO \qquad (26)$$

Substituted 2-oxazolines react with phenol or thiophenol in the absence of water to give ethers and thioethers (28).

eg;



$$+ \quad PhOH \xrightarrow[\Delta]{} PhCONHCH_2CH_2OPh \qquad (27)$$

Table II

Physical Properties of the Monomers[a]

Monomer	MW	BP(°C) (1 atm)	Density (g/mL)	pK_a(25°C)
Acrylic acid	72.06	139	1.051	4.25[b]
2-Methyl-2-Oxazoline	85.11	111	1.015	5.5[c]
-Propiolactone	72.06	162 decom (51,10 mm)	1.1406	-
2-Oxazoline	71.08	98	-	-

[a]All data from ref 36 unless otherwise indicated .

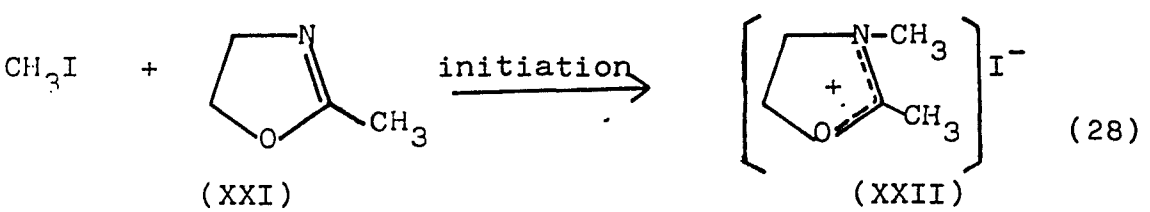
[b]From ref 37.

[c]From ref 38.

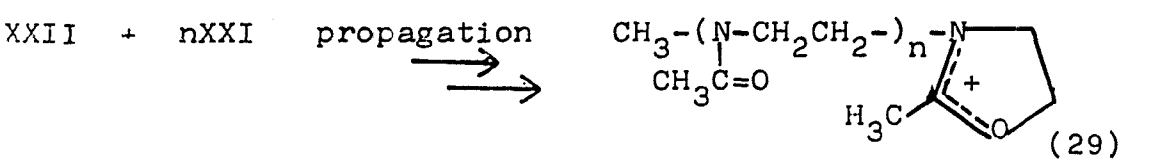
3.1 POLYMERIZATION OF 2-OXAZOLINES

Apart from the copolymerization of 2-oxazolines with electrophilic monomers (zwitterion polymerization) cationic homopolymerization of these monomers have been reported.2-Methyl-2-oxazoline undergoes polymerization with catalysts such as $SnCl_4$(32) ,$SbCl_5$, methyl iodide(33), methyl tosylate (34), $C_6H_5CH_2Br$ and $C_6H_5CH_2Cl$ (35) to give low molecular weight olegomers.

When MeI ,MeOTs or $\emptyset CH_2Br$ are used as initiators the propagating chain end is considered to be the correspondi-ng oxazolinium ion as shown in eq.28.



(XXI) (XXII) (28)

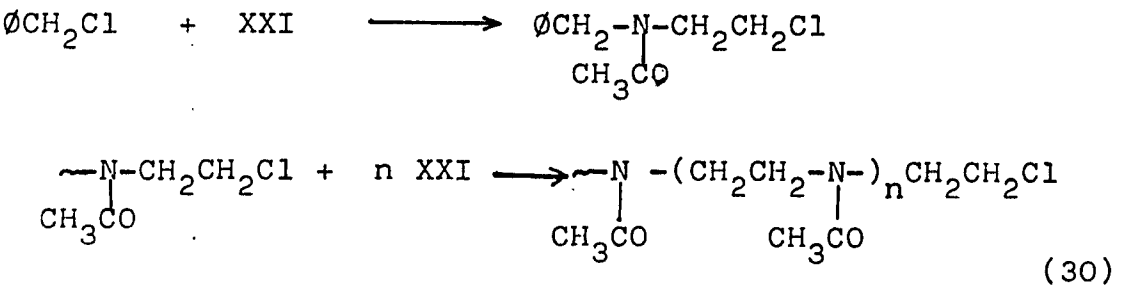


(29)

Results obtained in kinetic studies and direct NMR analysis of the reaction mixture has been given to support the above mechanism for the polymerization. Further , N-methyl-2-methyl-2-oxazolinium iodide and tosylate salts have been prepared as white crystalline materials which also can initiate the polymerization.

On the other hand when the nucleophile is strong such as Cl^-, the propagating end is covalent

N-acetyl-N-(2-chloroethyl) amino group. For example,the polymerization initiated by ϕCH_2Cl proceed by the following propagation mechanism.

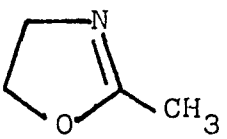
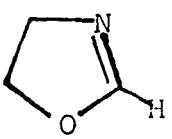
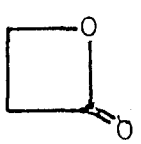


(30)

Similarly, 2-oxazoline also undergoes cationic polymerization with catalysts such as BF_3OEt_2,SbF_5, CH_3I and p-toluene sulfonic acid.However, metal chlorides such as $SnCl_5$,$SbCl_5$ are ineffective to initiate 2-oxazoline polymerization.

Table III

PMR and IR data of the monomers

MONOMER	PMR-Chemical shift(PPM)[a]	IR (cm^{-1})
Acrylic Acid	5.94(m,olefinic,3H)	3250(OH)
CH_2=CHCOOH	11.18(s,carboxylic,1H)	1735(C=O)
		1635,1620(C=C)
		1300(C-O)
		1190,990,920
2-Methyl-2-	1.92(s,CH_3)	2885,2908,2970,
Oxazoline		2930(C-H)
	3.66(m,N-CH_2)	1675(N=C)
	4.04(m,O-CH_2)	1345(C-Me)
		1228(C-O-C)
		985,938,898
2-Oxazoline	3.70(m,-N-CH_2)	2988,2912,2890(C-H)
	4.14(m,-OCH_2)	1635(C=N)
	6.8 (s,H)	1484,1350,1200,
		1090
β-Propiolactone	4.06(t,O-CH_2)	3030,2980,2930(C-H)
	3.38(t,CO-CH_2)	1835(C=O)
		1418,1324,1115,
		915

100-MHz PMR spectra for acrylic acid,2-methyl-2-oxazoline and 2-oxazoline were recorded in CD_3CN and β-propiolactone in DMSO-d_6. [a]Chemical shift in PPM from TMS.IR data (thin mull ,neat on a NaCl plate

4.0 EXPERIMENTAL

4.1 Purification of monomers and solvents

4.1a 2-Methyl-2-oxazoline (MeOXO)

2-Methyl-2-oxazoline (Aldrich) was first dried over anhy. Na_2SO_4(24 hrs.) followed by anhy. $MgSO_4$(24hrs.) The monomer was decanted into a flask containing activated molecular sieves 3A (5% w/v) and allowed to stand for seven days. Molecular sieves was activated prior to use according to the following literature reported procedure of Burfield et al (39). Molecular sieves ($3A^{\circ}$,8-12 mesh) was heated in an oven at $320^{\circ}C$ for four hours and cooled to room temperature in a desiccator before use.
After a second drying with a fresh batch of activated molecular sieves , the monomer was purified by distillation.A distillation apparatus with a built in vigreaux column and provision for collecting fractions without disturbing the distillation was used to distill the monomer.Before introducing the monomer into the distilling flask , the apparatus was flushed with dry nitrogen (after passing through two $CaSO_4$ drying towers) for half hour.The monomer was introduced into the distilling flask containing CaH_2. The distillation was carried out under a reduced nitrogen atmosphere while maintaining a pressure of about 5 torr . Under these conditions MeOXO distilled at $30^{\circ}C$. The receiving flask was cooled with dry ice/ acetone and the collected middle fraction was used for polymerization experiments.

The purity of MeOXO was checked with gas chromatography under the following conditions and no detectable impurity was found.

Gas chromatograph	Hewlett & Packard F & M Scientific 5750
Column	12 ft x ¼ inch 10% diethylene glycol succinate
Column Temperature	100°C
Injection port temperature	150°C
Carrier gas	Helium
Retention time	320 sec

4.1b Acrylic Acid

Acrylic acid (Aldrich) was dried using the same procedure used for drying MeOXO and the monomer was distilled using the same apparatus without any drying agent in the distilling pot. The distillation was carried out at a pressure of 5 torr under nitrogen atmosphere and the monomer distilled at 38°C under these conditions. The middle fraction was collected and used for polymerization experiments.

4.1c Acetonitrile and N,N-Dimethyl Formamide

Acetonitrile and DMF (Aldrich) were dried using the same procedure used for drying MeOXO. Acetonitrile was fractional distilled under nitrogen at atmospheric pressure (bp 80-81°C) and the middle fraction collected and used for polymerization experiments.

N,N-Dimethyl formamide was distilled under a reduced nitrogen atmosphere at 5 torr pressure with P_2O_5 in the distilling flask. DMF distilled at 57°C under these conditions and the collected middle fractions used for polymerization experiments.

4.1d β-Propiolactone (BPL)

β-Propiolactone (Fluka) was dried on molecular sieves 3A° (3 days, repeated twice) followed by CaH_2 overnight. BPL was distilled over CaH_2 under a reduced nitrogen atmosphere while maintaining a pressure of 5 torr. The middle fraction (bp 48°C at 5 torr) was collected and used for polymerization experiments.

4.1e Synthesis And Purification Of 2-Oxazoline (OXO)

The following literature reported (44) method was used to prepare 2-oxazoline.

Thionyl chloride (228 g , 1.91 mol) was added dropwise under cooling to a stirred solution of N-(2-hydroxyethyl)- formamide (170 g , 1.91 mol from Eastman) in 230 mL of DMF. The mixture was then heated at 40-45°C under reduced nitrogen pressure with nitrogen bubbling for 30 min and subjected to distillation under reduced pressure. N-(2-chloroethyl)-formamide was obtained as a colorless liquid (Yield 80%, bp 104-105°C at 3 torr).

To a 50% aqueous solution of potassium hydroxide (530 g), N-(2-chloroethyl)-formamide (160 g) was

added at 10°C with stirring. The mixture was kept at 15-18°C for about 5 min and crude OXO collected in a dry ice/acetone cold trap under 10 torr pressure. The distillate (110 g) was treated with potassium hydroxide (65 g) under cooling with ice. The dried OXO was distilled under reduced nitrogen atmosphere. The treatment with KOH was repeated to give 60 g of OXO, which was then treated with activated molecular sieves 3A° (seven days , repeated twice) followed by distillation under reduced nitrogen pressure (bp 23°C at 5 torr) with CaH_2 in the distilling pot.Yield 38%.

Reaction scheme;

$$HOCH_2CH_2NHCHO + SOCl_2 \longrightarrow ClCH_2CH_2NHCHO + SO_2 + HCl$$

$$ClCH_2CH_2NHCHO \xrightarrow{\text{aq. KOH}} \text{(OXO)} + KCl + H_2O$$

The purity of OXO was examined by gas chromatography under the following conditions and no detectable impurity was found.

Gas chromatograph	Hewlett & Packard F&M Scientific 5750
Column	5 ft x ¼ inch diethylene glycol succinate
Column temperature	100°C
Injection port temperature	150°C
Carrier gas	Helium
Retention time	172 sec

4.2 POLYMERIZATION METHODS

4.2a Method A

The polymerization was carried out by completely mixing the two monomers at time zero in a polymerization tube inside a dry box (N_2 atmosphere). A typical example is as follows.

2-Methyl-2-oxazoline (150 mmol) , acrylic acid (150 mmol) , p-methoxyphenol (0.8 mmol) and acetonitrile (15 mL) were mixed in a vessel inside a dry box and placed in a polymerization tube.The tube was cooled with liquid nitrogen , sealed under vacuum and then heated at 70°C for 48 hours.

4.2b Isolation And Purification of Copolymer

In all experiments the following general procedure was used to isolate the product copolymer

The reaction mixture was added dropwise into a large excess of anhydrous diethyl ether with stirring. The ether layer was decanted and the precipitated copolymer dissolved in methanol and reprecipitated into ether. The product was dried in a vacuum oven at 40°C for 48 hours.

4.2c Method B

The apparatus used to carry out the polymerization according to method B is shown in Figure 1. Monomers were placed inside two addition funnels (a and b in Figure 1) along with solvents when necessary under a nitrogen atmosphere.

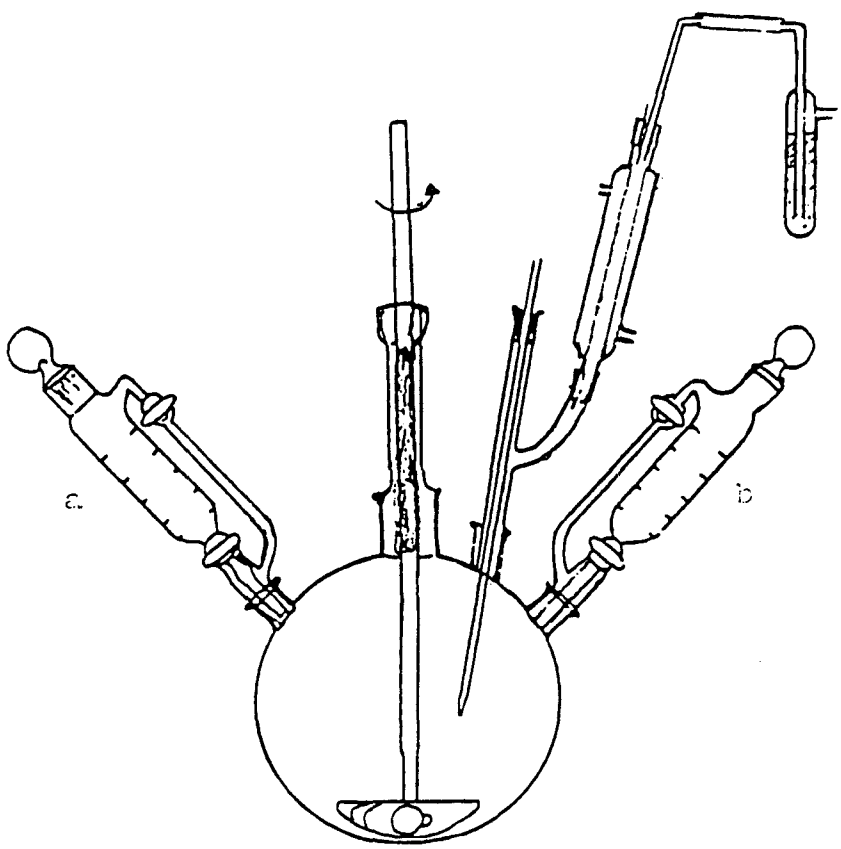


FIGURE 1. Apparatus used in polymerization Method B.

The 100 mL four necked round bottom flask was fitted with the two addition funnels , a mechanical stirrer, a condenser and a nitrogen inlet tube as shown in Figure 1. The reaction flask was heated to 70°C while passing dry nitrogen through the apparatus for a period of one hour. The monomers were added to the reaction flask maintained at 70°C over a period of four hours and further reacted at the same temperature for 44 hours.The polymer was isolated according to method 4.2b.

The same apparatus was used for the following experiments.

i). Slow addition of one monomer to the other.

ii). Addition of a nucleophile (NaOMe) to the reaction mixture.

iii). Addition of monomers over a very long period of time.

iv). Addition of monomers in three steps.

4.2d Method C

Figure 2 shows the apparatus used to distill monomers in a high vacuum manifold. The apparatus was custom made using teflon stopcocks (Rotaflow, supplied by Corning) capable of maintaining a vacuum of 10^{-6} torr. The apparatus was connected at V to a high vacuum system consisting of an oil pump , a mercury diffusion pump and a McLeod gage. The system was thoroughly heated with a hot air gun under vacuum until the McLeod gage reads a constant pressure of 10^{-6} torr.

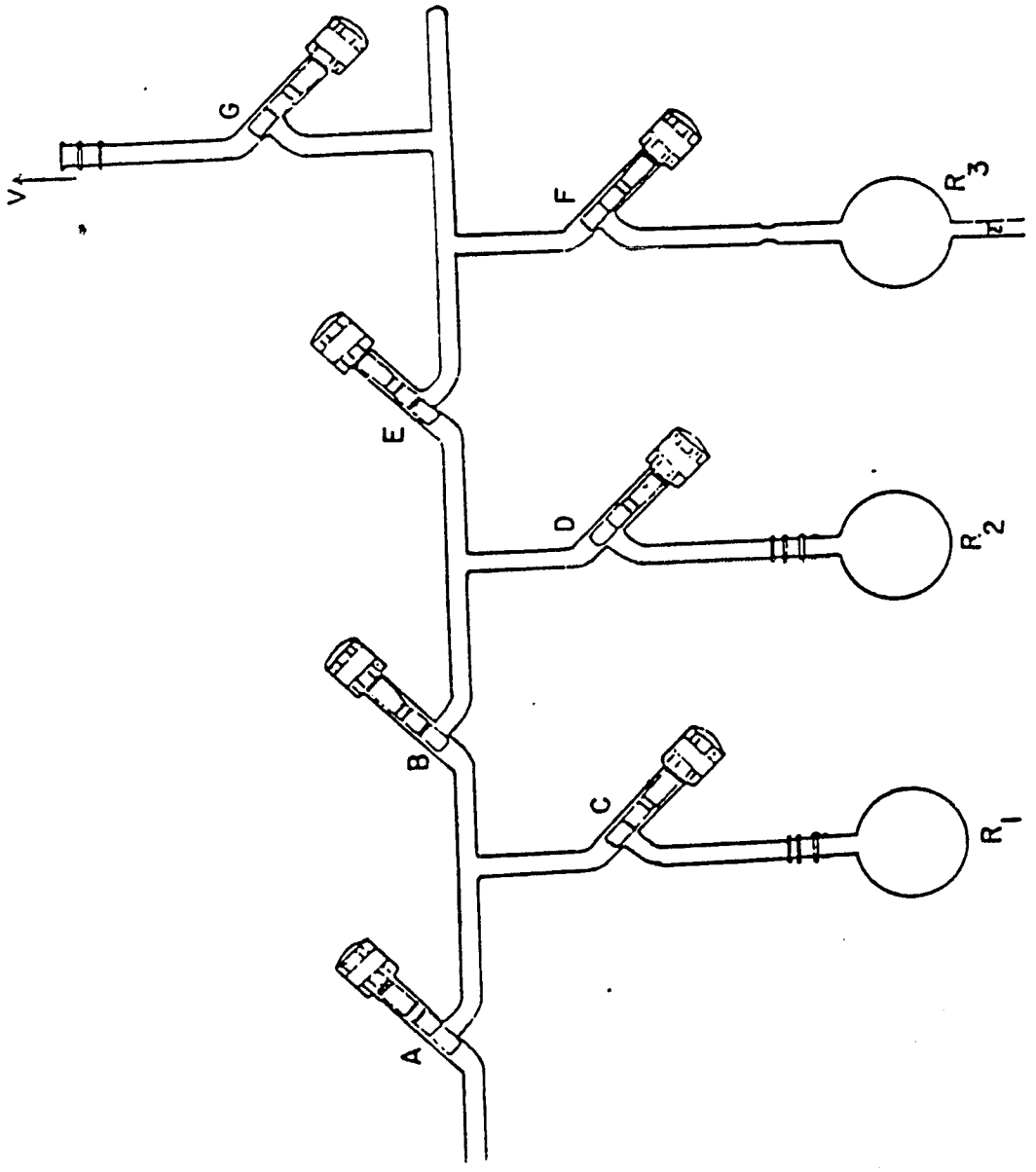


FIGURE 2. Apparatus used to distill monomers in a high vacuum manifold

Acrylic acid was initially dried and purified according to method 4.1b and introduced into flask R_1 with activated molecular sieves 3A° and a small quantity of radical inhibitor , p-methoxyphenol. The monomer was degassed and flash distilled to flask R_2 containing molecular sieves and radical inhibitor. Finally,acrylic acid was collected in ampoule R_3 where degassing was completed by pumping at 10^{-6}torr pressure.The ampoule R_3 fitted with Eck and Kreb breakable seal was sealed off with a fine point flame under continueous pumping and stored at 0°C until ready for use.

2-Methyl-2-oxazoilne was refluxed in flask R_1 over CaH_2 for three hours by connecting a reflux condenser between stopcock B and flask R_1. The monomer was flash distilled to flask R_2 containing CaH_2. After degassing, the monomer was finally distilled into R_3 where degassing was completed by pumping at 10^{-6} torr. The sealed ampoule was stored at 0°C until ready for use.

The required quantities of monomers were transfered into calibrated break seal tubes by using the apparatus shown in Figure 3 .Initially the ampoule R_3 containing the monomer was sealed to the apparatus and connected to the high vacuum line via V and degassed until the McLeod gage reads a constant pressure of 10^{-6} torr.The system was sealed off at the constriction .Required quantities of monomers were transferred to calibrated break seal tubes

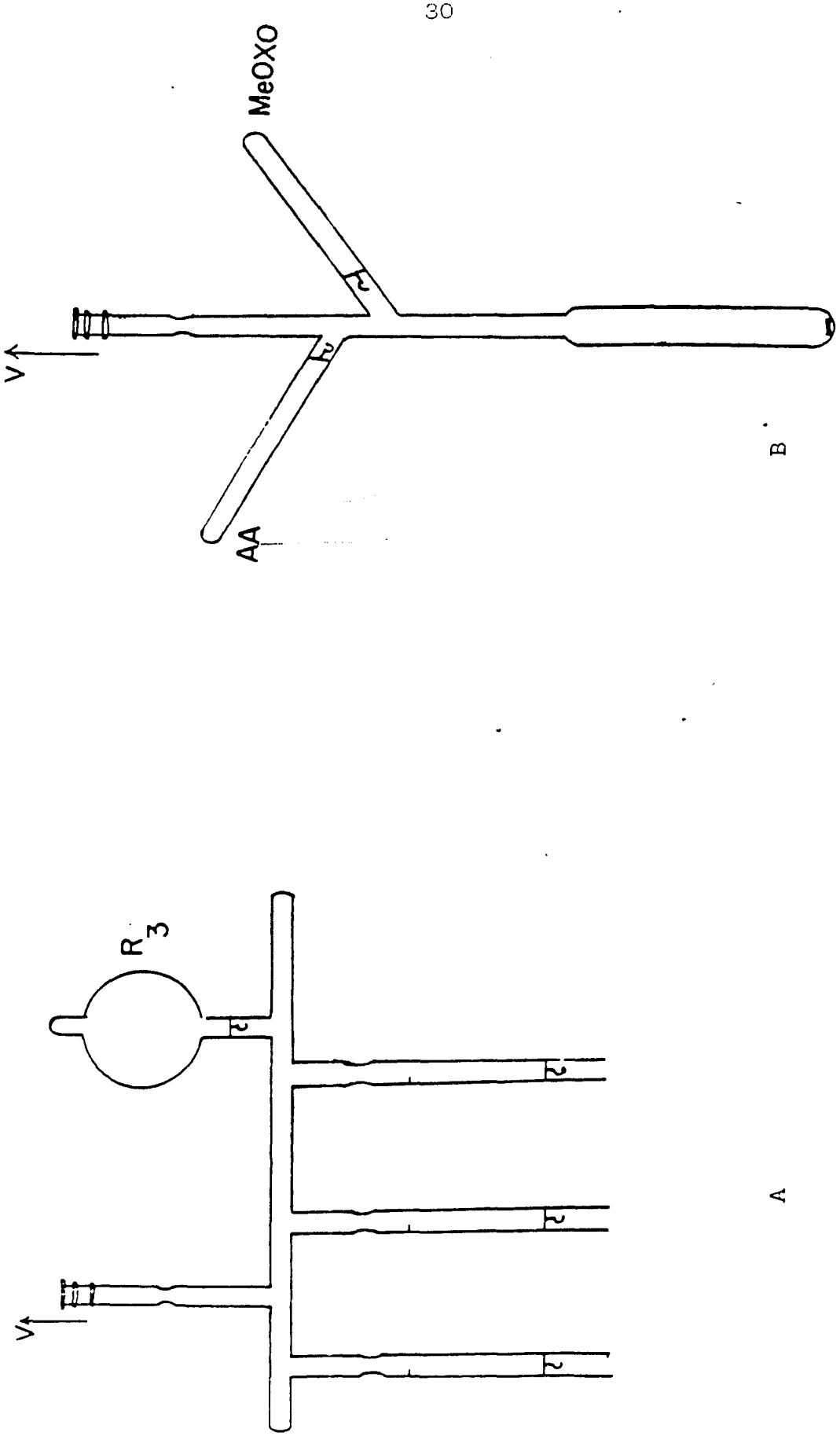


FIGURE 3. A: Apparatus used to transfer monomers into calibrated break-seal tubes.
B: Polymerization tube used in method C.

by breaking the seals at e and sealing off at the constriction . .

Ampoules containing the monomers were sealed to a polymerization tube which contained the radical inhibitor p-methoxyphenol , as shown in Figure 3. The monomers were mixed by breaking the seals and polymerization carried out by heating the tube at 70°C for 48 hours.The product copolmer was isolated and purified according to method 4.2b.

4.3 Molecular Weight Determination

The number average molecular weightsof copolymer samples were determined using a Hewlett & Packard vapor pressure osmometer model 302B at 55°C with water as the solvent. The instrument was calibrated with dextrose (MW= 180.16) as the standard compound. The typical concentration of copolymer samples ranged from 1 to 4%.

4.4 SPECTROSCOPIC ANALYSIS

4.4a 100 MHz Proton NMR

100 MHz proton NMR spectra of copolymers were recorded on a JEOL, JNH-MH-100 spectrometer. The concentration of polymer samples used ranged from 15-20% (w/v) in DMSO-d_6 (99.98% deuterated).

4.4b 300 MHz and 270 MHz Proton NMR

300 MHz and 270 MHz proton NMR spectra were recorded on Nicolet / Oxford NT 300 and IBM WP270SY spectrometers respectively. Spectra were recorded from DMSO-d_6 (100% deuterated) solutions.

Polymer samples (6-8 mg) was dissolved in 0.5 mL of DMSO and filtered through glass fiber filter paper before recording the spectra.

4.4c Infrared spectroscopy

The IR spectra were recorded on a Beckmann 4260 spectrometer.The copolymer (2 mg) was dissolved in methanol (0.2 mL) and deposited on a NaCl plate as a thin film . The NaCl plate was dried in a Vacuum oven at 40° C overnight and IR spectrum recorded immediately.

4.4d Natural Abundance ^{13}C NMR Spectra

Natural abundance ^{13}C spectra of copolymer samples were recorded on a IBM NR/80 spectrometer operating at 20.1 MHz . Spectra were obtained from deuterium oxide (20% w/v) with CH_3CN as the internal standard.Polymer samples were filtered through glass fiber filter paper before recording spectra.A single frequency off resonance decoupling experiment (SFOR) was done by shifting the 02 value from 6540 (value used for BB decoupling) to 4300 . Under these conditions , the protons directly attached to the carbon atom can split the ^{13}C NMR signal for that carbon atom.

4.5 Hydrolysis of Copolymer

The copolymer was hydrolyzed to aid in its identification . Figure 4 shows the procedure used to isolate and identify the various hydrolysis products. The copolymer (1.0 g) was refluxed in 10% aqueous NaOH at 100°C for three hours , the hydrolyzate acidified to pH 3

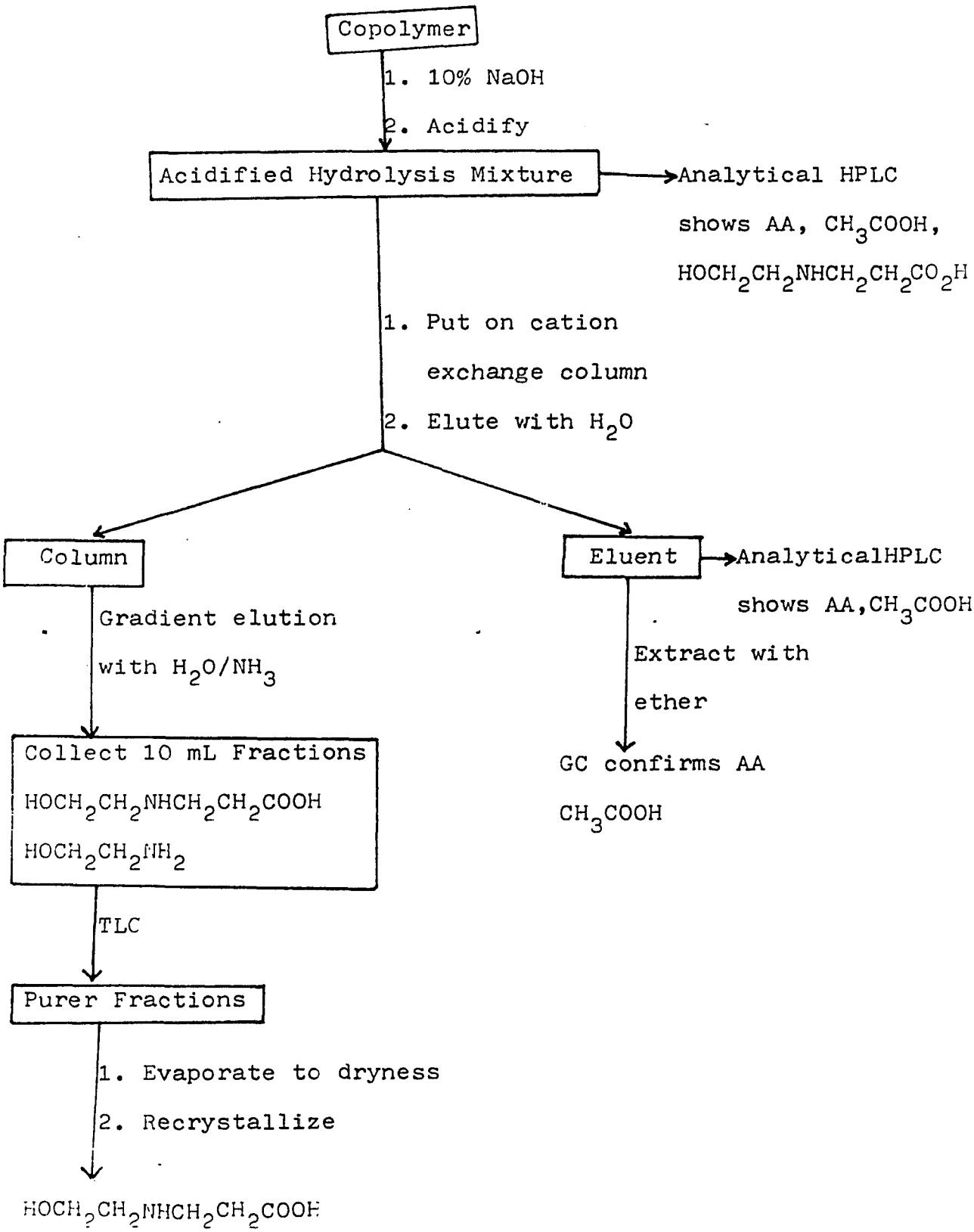


Figure 4. Alkaline hydrolysis of MeOXO-AA copolymer.

and a portion subjected to analytical HPLC. The remainder of the acidified hydrolyzate was introduced onto a cation exchange resin column (Dowex 50 x 8-400) which was prepared by the following method. Dowex resin (15 g) was washed with 100 mL of 2.5 N sodium hydroxide followed by distilled water until the washings are neutral to litmus paper. The resin was further washed with 100 mL of 2.5 N HCl followed by distilled water until the washings showed no precipitate with an aqueous solution of $AgNO_3$. The washed resin was packed into a 30 X 2 cm glass column fitted with a teflon stopcock.

The resin column after introducing the acidified hydrolyzate was eluted with water.Three 100 mL fractions were collected and analyzed by HPLC. The combined fractions were extracted with two 100 mL portions of diethyl ether by stirring for several hours.The combined ether layers were concentrated to about 3 mL and analyzed by gas chromatography under the following conditions.

Gas chromatograph	Hewlett & Packard F&M Scientific 5750
Column	5 ft x ¼ inch ethylene glycol succinate
Column temperature	130 ^{o}C
Injection port temperature	185 ^{o}C
Carrier gas	Helium
Retention times	Acetic acid; 165 sec Acrylic acid; 345 sec

The cation exchange resin column was further eluted with two 500 mL solutions of aqueous ammonia having pH 10 and 11 by using a gradient elution method. 10 mL fractions were collected and analyzed by thin layer chromatography using water: n-butanol : pyridine ; acetic acid (15: 12 : 10 : 2) solvent system.Thin layer chromatography of the various eluent fractions with ninhydrin showed there were two components present with one component present in much greater amount than the other. Most fractions contained only the major component N-(2-hydroxyethyl)-β-alanine. These fractions were collected together , evaporated to dryness , recrystallized from methanol -acetonitrile to give a white crystalline solid (mp 146°C). and analyzed by proton NMR in D_2O. The minor component , ethanolamine , was isolated in a separate experiment .

4.6 Benzoylation of Hydrolysis Mixture

In another hydrolysis experiment , the copolymer (0.5 g) was refluxed with 10% sodium hydroxide at 100°C for three hours. After the hydrolysis is complete another 5 mL of 10% NaOH was added to the reaction mixture . Under cooling (0°C) and stirring, benzoyl chloride (1.5 g) was added to the reaction mixture dropwise and a light yellow precipitate was obtained. The reaction mixture was extracted with three 10 mL portions of methylene-chloride. (Under these conditions , N-(2-hydroxyethyl)-β-alanine should undergo benzoylation but the product

would be soluble as the carboxylate salt.) The combined methylene chloride layer was extracted first with a 20 mL portion of dil HCl followed by distilled water.The dried methylenechloride layer upon evaporation gave 0.094 g of a solid material.Analytical HPLC showed that this material to contain the dibenzoyl derivative of ethanolamine and another compound. The dibenzoyl derivative was purified by analytical HPLC on a μBondapak C_{18} column using methanol: H_2O : TFA : (550 : 450 : 0.6, v/v/v) as the mobile phase to give 20 mg of a white solid material with a mp of 82°C. The 100 MHz proton NMR of the product was recorded in $CDCl_3$ with TMS as the internal standard.

4.7 Bromination of the Copolymer

A solution of bromine in methanol was added dropwise under cooling (0°C) to a solution of copolymer until a yellow color is produced. The solution was stirred at room temperature for one hour and solvent evaporated under vacuum to give a light yellow solid which was dried overnight in a vacuum desiccator and 100 MHz proton NMR recorded in DMSO-d_6.

4.8 PREPARATION OF AUTHENTIC COMPOUNDS

4.8a Preparation of N-Methyl-2-Methyl-2-Oxazolinium Iodide

The following literature reported (33) procedure was utilized.

To a stirred solution of methyl iodide (8.52 g , 60 mmol) in ether (10 mL) was slowly added 2-methyl-2-

oxazoline (1.28 g , 15 mmol) at 5°C . The solution was stirred at 20°C for one hour to give a white precipitate which isolated by filtration and washed with ether. The solid was further purified by recrystallization with CH_3CN/ether (mp 145°C , Lit. mp 144-146°C)

4.8b N-(2-Hydroxyethyl)-β-alanine

The following literature reported procedure (45) was used.

Ethanolamine (0.022 mol, from Aldrich) was added dropwise into a stirred solution of β-propiolactone (0.01 mol, from Fulka) in acetonitrile over a period of about two hours , while maintaining the temperature at 0°C. The precipitated solid was filtered , dried and recrystallized from methanol to give a white crystalline material with a mp of 146°C (Lit mp 145-147°C).

4.8c Dibenzoyl Derivative of Ethanolamine

Benzoyl chloride (5 g) was added dropwise under cooling and stirring to a solution of ethanolamine (0.6 g) in 10% sodium hydroxide (10 mL) . The reaction mixture was acidified and the resulting white solid recrystallized with ethanol/water to give a crystalline solid with a mp of 82°C.

4.9 HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

4.9a Analytical HPLC

High performance liquid chromatography was carried out on a Waters system consisting of M-6000

solvent delivery unit and a U6K universal liquid chromatography injector, coupled to Waters 450 variable wave length UV moniter with an 8-µL flow through cell. The µBondapak C_{18} column (10 µm , 30 cm x 0.39 cm ID) was also from Waters Associates. Sample injections were made with a 25 µL syringe (Hamilton) . Filtration of solvents was carried out using a pyrex filter holder (Millipore) . All solvents used were of HPLC grade (Fiher) ; water was glass distilled. Generally a flow rate of 2 mL/min was maintained by a pressure of 2000-2500 psi. The recorder chart paper speed was 1/2 inch/min. All tests were performed at room temperature, Sample sizes varied between 1 and 10 µg of polymer material injected in volumes of 1-25 µL . Detection was usually at 210 nm. The sensitivity of the UV detector was set at 0.1 AUFS (absorbance units for full scale).

4.9b Fractionation of Copolymer by preparative HPLC

A Waters Prep LC / system 500 was used for the fractionation of the copolymer. µBondapak C_{18} column was used with the solvent system , methanol : water : trifluoroacetic acid (350 : 650 : 0.8 , v/v/v) . The solvents used were of reagent grade. A solution of copolymer (2 g) in 20 mL of HPLC solvent system was injected to the column and eluted at a flow rate of 100 mL/min . 50 mL portions of the eluent were collected and examined by analytical HPLC for purity. Impure portions (fractions with more than one component) were discarded. Pure fractions (i.e

fractions containing one component as determined by HPLC) of the same component were combined , concentrated in a Rotovapor evaporator under reduced pressure to a volume of 10 mL and freeze dried. During the evaporation of solvent , the distilling pot was kept in a water bath maintained at 45°C.Freeze dried fractions were further dried in a vacuum oven at 40°C and in a vacuum desiccator overnight each. 300 MHz proton NMR spectrum of each isolated fraction was recorded in DMSO-d_6(100%) with TMS as the internal standard.NMR spectra were recorded immediately after the samples were prepared.

4.10 Direct NMR Analysis of Reaction System.

The following general procedure was used to prepare samples for direct NMR analysis experiments.

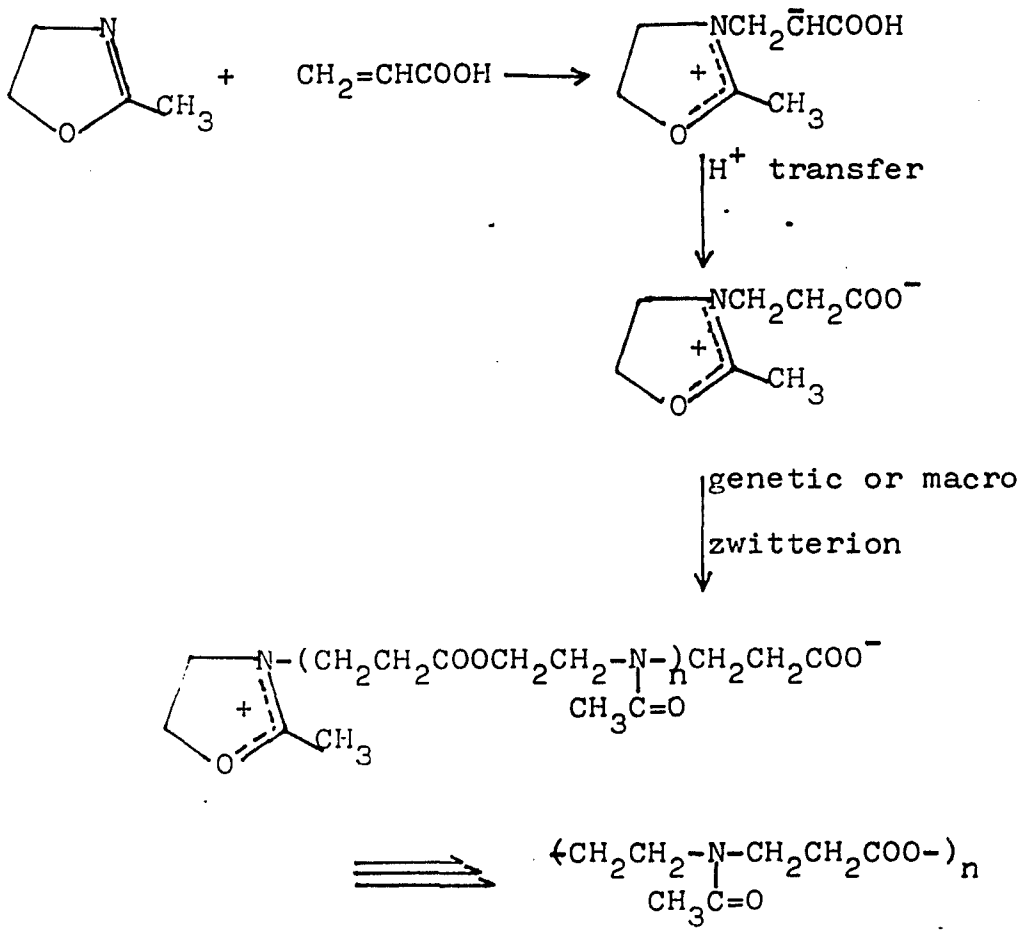
The monomers and solvents were purified as described in section 4.0. 2-Methyl-2-oxazoline (11.8 mmol), acrylic acid (11.8 mmol) , p-methoxyphenol (0.06 mmol) and deuterated acetonitrile (1.5 mL) were mixed in a vessel inside a dry box. A sample of the reaction mixture (0.5 mL) was placed in a NMR sample tube with a small amount of TMS as the internal standard. The NMR tube was sealed under vacuum . The 100 MHz proton NMR spectrum of the reaction mixture was recorded at room temperature after reacting at 60°C for different time intervals.

The same procedure was used for experiments involving the monomer system , 2-oxazoline and acrylic acid.

5.0 RESULTS AND DISCUSSION

5.1 Molecular weight of copolymer

We have studied the copolymerization of 2-methyl-2-oxazoline and acrylic acid under different reaction conditions with the objective of synthesizing high molecular weight copolymers. The rational for our experimental approach is based on the reaction mechanism proposed by Saegusa and coworkers which is illustrated in the following reaction scheme.



The initially formed genetic zwitterion can be considered as the bifunctional reagent in an A-B type of step polymerization ... analogous to the polymerization of

an amino acid or hydroxy acid with itself. On this basis, by careful purification of monomers and solvents and carrying out the reaction to high conversion under inert atmospheric conditions to prevent termination of growing macrozwitterions by adventitious species , one should be able to improve the molecular weight of copolymer.Careful considerations were given in this study to dry and purify monomers and solvents. Results reported by Burfield and coworkers (39-43) were utilized to find optimum desiccants and conditions for drying monomers and solvents. We have investigated three main methods to carry out the polymerization reaction.Methods A and B employed the usual methods of purification of materials by vacuum distillation and carrying out the polymerization ; Method C employed a high vacuum system.Polymerization by Method C would involve lower concentration of adventitious impurities such as H_2O, CO_2, and NH_3. Method A involved the rapid initial mixing of MeOXO and AA followed by their reaction.Method B involved variations of Method A in which the monomers were slowly added together, one monomer slowly added to the other, the reaction carried out in stages , or nucleophile added.

Table IV shows a comparison of the results from Methods A ,B and C. Although Saegusa and coworkers (14) reported only the solution polymerization of MeOXO-AA , we have observed that polymerization also occur in bulk. The bulk polymerization yielded the higher molecular weight product for Method A although there was no difference

for Method B. The lower molecular weight products were white semisolids with solubility in water, methanol, DMF and DMSO. The higher MW products were white solids with the same solubility characteristics. The highest MW (2760) obtained was for a copolymer made by method C indicating that adventitious impurities participate in termination but the effect was not large. Method B generally gave slightly higher molecular weights than method A. When polymerization was carried out in bulk a small fraction (5-10%) of the product was insoluble whereas the product is completely soluble under other polymerization conditions. The work reported in this thesis on polymer characterization relates only to the soluble product.

Increasing the polymerization temperature to 100°C significantly decreased the polymer molecular weight as well as the yield.The use of DMF as solvent instead of acetonitrile resulted in lower molecular weight. Similar results were observed by Saegusa and coworkers (10) who reported $\bar{M}_n$ values of 1600 and 1400 , respectively, for MeOXO-AA polymerization in acetonitrile and DMF. Overall, the molecular weight data in Table IV clearly shows that even when reaction conditions (Method C) are choosen to avoid adventitious terminating agents from the atmosphere as well as those present as impurities in the monomer , there is no large improvement in the copolymer MW.

Table IV

Comparison of Methods A,B and C for MeOXO-AA polymerizzation[a]

Polymerization method	Temperature, °C	Yield,[d] %	$\bar{M}_n$
A (solution[b])	70	45	1450
A (solution[c])	60	51	920
A (bulk)	70	55	1850
B (solution[b])	70	60	2000
B (bulk)	70	69	1960
B (bulk)	100	21	590
C (bulk)	70	41	2760

[a] p-Methoxyphenol present in all experiments

[b] Solution polymerization in CH_3CN

[c] Solution polymerization in DMF

[d] Yield of recrystallized polymer.

Method B was used to study the effect of variations in the reaction conditions on molecular weight (Table V) .The standard conditions (experiment 1) involved the simultaneous additions of MeOXO and AA to the reaction flask over a four hour period followed by heating for an additional 44 hours. This compares with method A in which the two monomers were rapidly mixed

together and then heated for 48 hours. The purpose of the slow addition was to keep the concentration of propagating centers low so as to increase the copolymer molecular weight. Experiment 1 showed some increase in yield and molecular weight relative to method A. However, when the monomer addition period was increased to two days (Experiment 8) and one week (Experiment 9) , both the yield and molecular weight decreased significantly. If the propagating centers remain active for a long period of time , these experiments should have led to increased molecular weight. The lowered molecular weights indicate the growing macrozwitterions undergo termination during these long addition times. Experiment 4 involved the quick addition of monomers followed by a 12 hour reaction time. The copolymer yield and molecular weight were comparable to those obtained at the standard reaction time of 44 hours. Experiment 5 involved a three stage polymerization in which one-third each of the MeOXO and AA were quickly mixed , reacted for 12 hours, followed by two fresh batches of monomer quickly added in sequential fashion with a 12 hour reaction time following each addition. No improvement in copolymer molecular weight was observed while the yield actually decreased. Even if the polymer chains have only one of the two active ends still active, this experiment should have yielded higher molecular weights since a fresh batch of the monomers can produce genetic zwitterions which could add

Table V

Variation of Method B for MeOXO-AA Polymerization

Experiment	Polymerization Conditions[a,b]	Yield[c],%	$\bar{M}_n$
1	Standard[d]	69	1960
2	MeOXO present initially, AA added slowly[d]	60	1430
3	AA present initially, MeOXO added slowly[d]	50	1170
4	Standard[e]	64	1910
5	Monomers added in 3 stages[f]	41	1940
6	2.6 mol-% CH_3ONa added at start of reaction[d]	61	1200
7	1 mol-% CH_3ONa added after 50% of monomers added[d]	73	1660
8	Monomers added over a period of 2 days	20	1110
9	Monomers added over a period of 1 week	8	900

[a]Bulk polymerization at 70°C with both monomers being simultaneously added unless otherwise noted.

[b]All experiments involved equimolar amounts of MeOXO and AA with p-methoxyphenol added to AA.

[c]Yield of recrystallized polymer.

[d]Monomer(s) added over 4 hours and then reacted for additional 44 hours.

[e]Monomers added quickly and then reacted for 12 hours.

[f]One-third of MeOXO and AA added in each stage followed by reaction for 12 hours.

to the active end of the polymer chain . Thus, we conclude that the MeOXO-AA system does not behave as one with living characteristics.

Experiments 2 and 3 were carried out with a view of ascertaining whether one or the other of the two monomers was solely responsible for termination reactions which limit molecular weight. One monomer was placed in the reaction flask and the other then added over a 4 hour period followed by reaction for an additional 44 hours.The decrease in copolymer molecular weight in both experiments indicates the involvement of both AA and MeOXO simultaneously in terminating the propagating macrozwitterions. Control experiments were also carried out to ascertain whether either MeOXO and AA undergoes homopolymerization under our experimental conditions.A small amount of one monomer was added to the other , the reaction mixture heated for 48 hours and worked up in the usual manner . No polymer was formed under these conditions . In other experiments (Experiments 6 and 7) we investigated the effect of adding sodium methoxide to the reaction mixture on the copolymer molecular weight. Addition of $NaOCH_3$ did not result in higher molecular weights as reported in some zwitterion polymerizations (26,27). The molecular weight decreased relative to that obtained in the absence of sodium methoxide. In both cases about 10% of the product copolymer was found to be insoluble in the solvents, that the copolymer is normally soluble.The purpose of adding

sodium methoxide was to terminate oxazolinium end of a growing macrozwitterion and to keep the carboxylate end active which may react with the genetic zwitterions to increase the size of the polymer chain.However, the presence of large amounts of unreacted acrylic acid in the medium which can react with the added sodium methoxide may prevent it from reacting with the growing macrozwitterions. If there were only zwitterions, genetic or macro in the reaction medium , this method would have helped to obtain high molecular weight copolymers.

We have investigated a large number of different approaches to increase the copolymer molecular weight . The lack of any significant improvement in molecular weight indicates that the both monomers are simultaneously involved in limiting the copolymer molecular weight.

5.2 Copolymerization of 2-Oxazoline(OXO) with β-Propiolactone (BPL) and Acrylic Acid (AA)

We attempted to obtain high molecular weight copolymers from the OXO-AA monomer system for which Saegusa and coworkers (10) obtained a MW of 13,500. These two monomers polymerized in solvents such as acetonitrile or in bulk to give light yellow colored gummy materials. However, when the polymer was purified by precipitation into ether and dried the resulting rubbery product became insoluble in solvents such as water , methanol and DMF and formed a gel

when attempted to dissolve in these solvents. Saegusa and coworkers (10) have indicated that the OXO-AA copolymer was only partially soluble in D_2O , the solvent they used for proton NMR analysis.Due to this solubity problem , we did not determine the $\bar{M}_n$ for this copolymer. The reported high molecular weight by Saegusa and coworkers may be as a result of this solubility problem.

Polymerization of OXO-BPL system also gave light yellow colored gummy materials. The MW obtained was

Table VI

Polymerization of OXO with BPL and AA [a]

Monomer system	Polymerization method	Temp. °C	Time, hours	Yield[e], %	$\bar{M}_n$
OXO-BPL	A[b]	30	28	64	795
OXO-BPL	B[c]	25	28	63	708
OXO-AA[d]	B[c]	55	24	51	-
OXO-AA[d]	B[c]	75	24	48	-
OXO-AA[d]	A[b]	60	30	52	-

[a] All polymerizations involved equimolar amounts of the two monomers (44 mmol each).

[b] Solution polymerization in acetonitrile.

[c] Bulk polymerization, monomers added slowly for four hours and reacted for 24 hours.

[d] 0.53 Mol-% of p-methoxyphenol added to AA.

[e] Yield for recrystallized polymer.

considerably low (see Table VI) compared to that obtained by Saegusa ($\bar{M}_n$ = 3500) However , OXO-BPL system did not show the solubility characteristics shown by the OXO-AA system. The OXO-BPL polymer was found to be soluble in solvents such as water, methanol, DMF and DMSO. Inability to obtain higher molecular weight copolymers from these monomer systems may indicate the involvement of monomers themselves in termination reactions similar to the MeOXO-AA monomer system.

6.0 SPECTROSCOPIC CHARACTERIZATION OF COPOLYMER

6.1 Proton NMR Spectra

A MeOXO-AA copolymer ($\bar{M}_n$ = 1452) prepared by method A using acetonitrile as the solvent was used for characterization experiments.Figure 5 shows the 300 MHz FT proton NMR spectrum of the copolymer recorded in DMSO-d_6 (100% deuterated) .Similar results were obtained at 270 MHz. The NMR signals at 12.25 PPM and 7.95 PPM have been assigned for carboxylic (-COO<u>H</u>) and amide (-<u>N</u>HCO-) protons, respectively, based on the chemical shift values and their behavior in the presence of D_2O.When the NMR is recorded in DMSO in the presence of a small amount of D_2O, both these signals disappear due to exchange between hydrogen and deuterium. The multiplet centered at 6.15 PPM is assigned to olefinic protons of the group CH_2=CHCOO-. Figure 6 shows the expanded spectrum in which this signal can be seen as three sets of multiplets for the three different protons of the olefinic group as expected. This assignment is confirmed by the proton NMR of the brominated copolymer. The brominated copolymer shows no signals in the region between 4.5 PPM and 7.95 PPM as the -OOCCHBrCH_2Br protons absorb upfield of 4.5 PPM.

Consider the structure $-(CH_2CH_2-\underset{\underset{CH_3C=O}{|}}{N}-CH_2CH_2COO)_{\overline{n}}$

as the the repeating unit structure of the copolymer. We would expect four multiplets for the methylene protons of

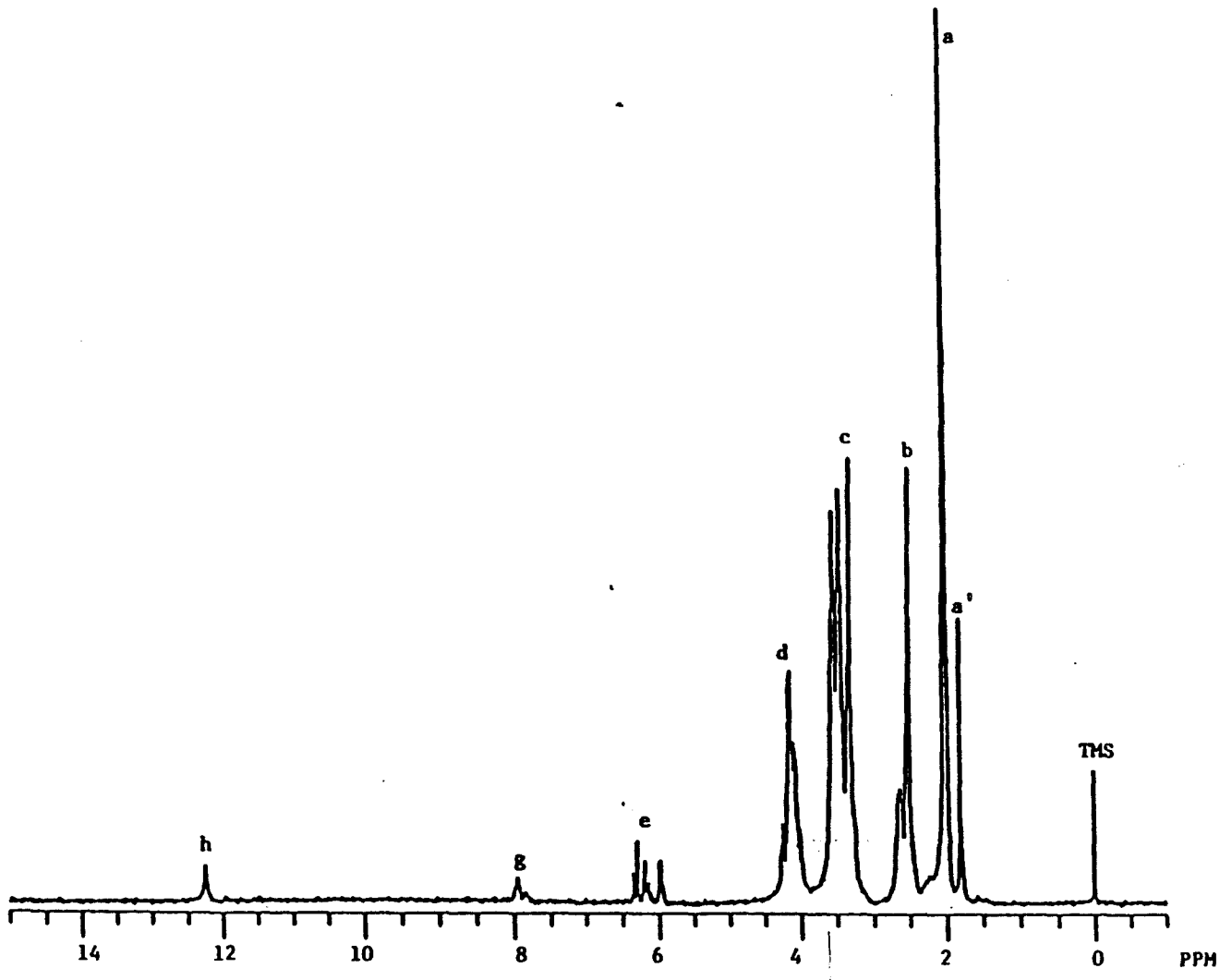


FIGURE 5. 300 MHz proton NMR spectrum of MeOXO-AA copolymer. Conditions: 1.8% w/v in DMSO-d_6 (100%) ; 70° pulse angle ;25°C ; 6.7 sec. delay between pulses; 258 scans ; TMS internal standard.

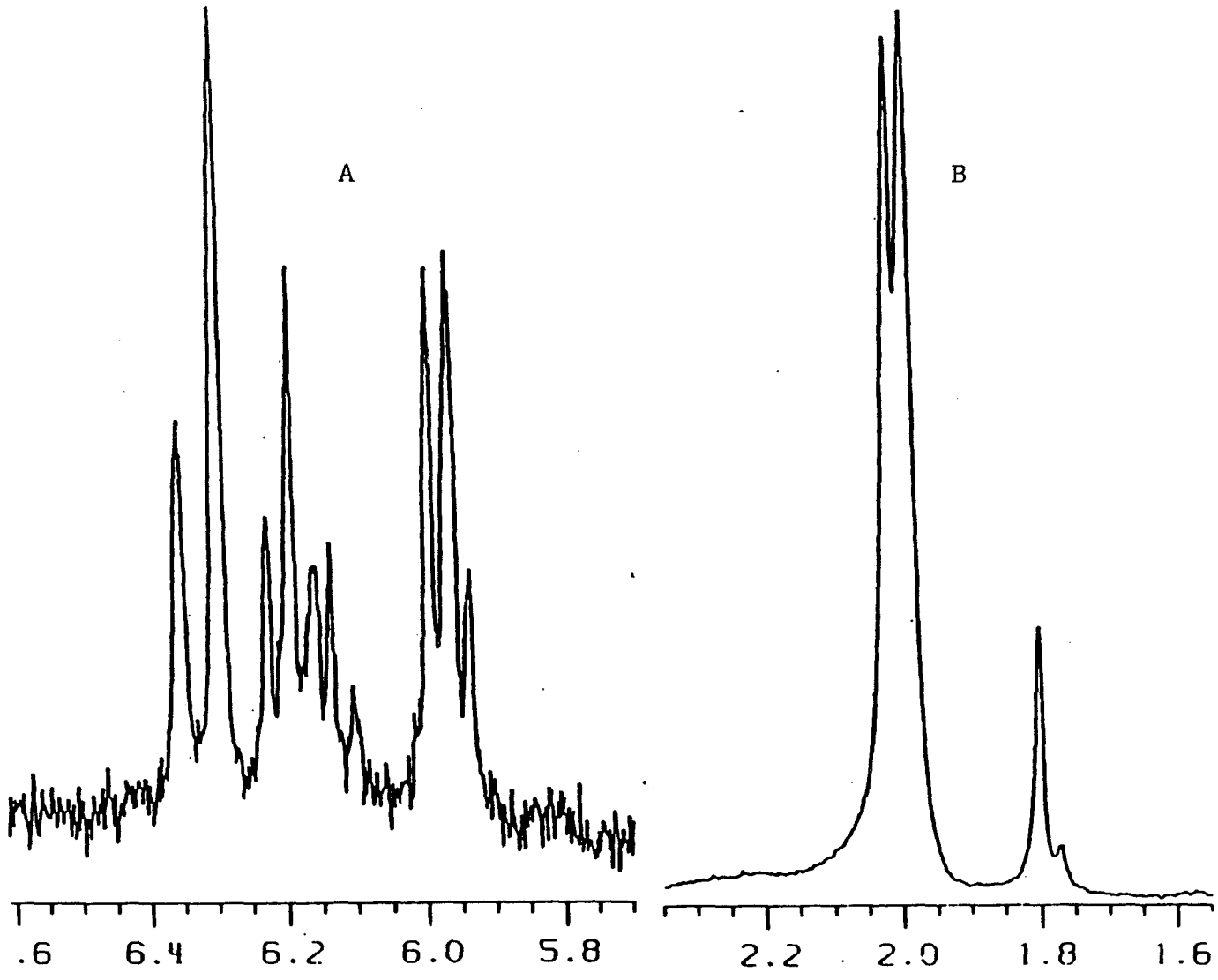


FIGURE 6. A: Expanded olefinic region. B: Expanded methyl region.

main chain and another signal for the side chain methyl group.The observed NMR signals are assigned as follows.

Chemical Shift (PPM)	Assignment
1.80	Singlet, $-NHCOC\underline{H}_3$
2.0	Doublet, $-NCOC\underline{H}_3$
2.50	Multiplet, $C\underline{H}_2CO_2-$
3.45	Multiplet, $C\underline{H}_2-N-C\underline{H}_2-$
4.13	Multiplet, $CO_2C\underline{H}_2-$
6.15	Multiplet, $C\underline{H}_2=C\underline{H}COO-$
7.95	Singlet, $-N\underline{H}COC\underline{H}_3$
12.25	Singlet, $-COO\underline{H}$

Although Saegusa and coworkers (14) reported proton NMR data for the MeOXO-AA copolymer , no mention was made of the presence of signals for carboxylic, olefinic and amido protons. Saegusa and coworkers reported NMR data showing only CH_3CO, CH_3CO_2, $CH_2NCH_2$and CO_2CH_2; no actual spectrum was present in that paper.They proposed the 1:1 alternating structure based on the NMR data and elemental analysis results.Balakrishnan and Periyasamy (29) reported the NMR of MeOXO-MAA copolymer in D_2O. Except for the indicated presence of two weak doublets at 5.2 PPM for olefinic protons no mention was made of $-N\underline{H}$ and $-COO\underline{H}$ signals.The proposed 1:1 alternating structure,

$$-(CH_2CH_2-\underset{\underset{CH_3C=O}{|}}{N}-CH_2\underset{\underset{CH_3}{|}}{C}HCOO)_n$$

is not consistent with the NMR data reported.The published

spectrum shows the signal areas for the two methyls at 1.95 PPM ($-C-CH_3$) and 2.05 PPM ($-COCH_3$) to be about 1:2 instead of 1:1 as it would be for the alternating copolymer.

Since we observe considerably more detail than previously reported for the proton NMR of the MeOXO-AA copolymer, a detailed discussion of the results is worthwhile. The NMR signals for the methylene groups of the repeat unit and the side chain methyl group become complicated as a result of the restricted rotation around the C-N bond of the amide group. The methyl group protons appear as a pair of closely spaced singlets at 2.0 PPM instead of one singlet. If there were free rotation around the C-N bond , the methylene groups should appear as four triplets. Restricted rotation results in four pairs of triplets for the four methylene groups. However, this detail is not sufficiently clear in the observed spectrum. The low molecular weight of the copolymer , presence of different end groups and molecular weight polydispersity further complicate the NMR spectrum at a high field such as 300 MHz. For example, the repeat unit adjacent to an end group can experience a slightly different NMR environment compared to the other repeat units.

The difference in environment resulting from restricted rotation around the C-N bond can be overcome by recording the NMR at a higher temperature. Figure 7 shows

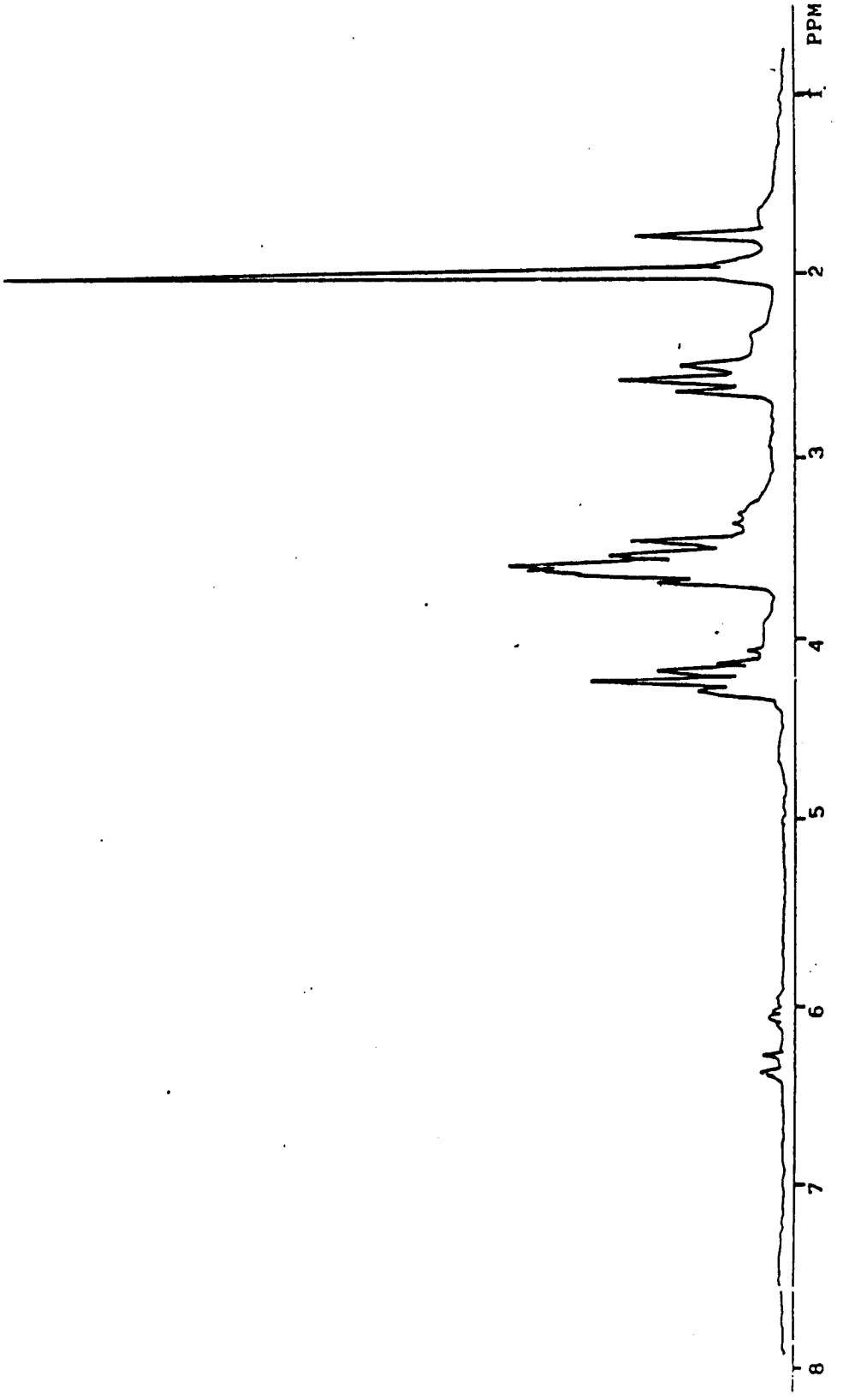
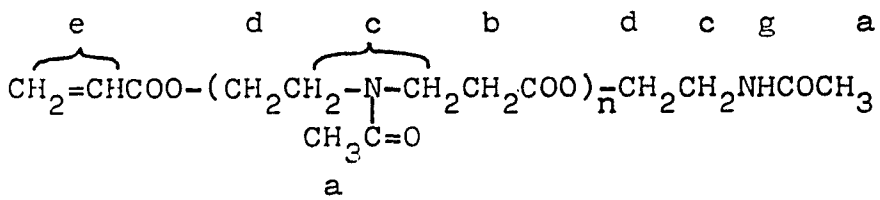


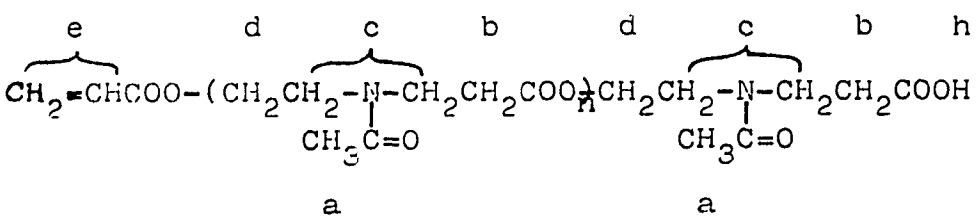
FIGURE 7. 100 MHz proton NMR of MeOXO-AA copolymer. Conditions: 8% w/v in DMSO-d_6(100%); 150°C.

the 100-MHz spectrum of the copolymer recorded at 150°C. The methyl group signal has changed to a sharp singlet . The CH_2-COO signal is now a triplet as expected. The two methylenes attached to nitrogen , CH_2-N-CH_2, appear as two overlapping triplets with some additional signals which probably arise from end groups, e.g.,-$OCH_2CH_2NHCOCH_3$. Similarly , the-COO-CH_2 protons appear as a triplet with additional signals arising from the end groups.

Overall, our NMR spectra show strong qualitative evidence for the 1:1 repeat unit ($-CH_2CH_2-\underset{\underset{CH_3C=O}{|}}{N}-CH_2CH_2COO-)_n$ and carboxylic (COOH) , olefinic (CH_2=CH-COO) , and acetamido (CH_3CONH) end groups. The following two structures are proposed for the MeOXO-AA copolymer.



(XXIIIa)



(XXIIIb)

The 270 MHz and 300 MHz proton NMR results were used to calculate the degree of polymerization (Table VII) and copolymer composition (Table VIII) .

Table VII

Degree of Polymerization of MeOXO-AA Copolymer

NMR Conditions	DP Calculated from comparison of e protons with protons					
	a	b	c	d	(a+b+c+d)	(a'+a+b+c+d)
300 MHz 70°/6.7 sec[a]	17.6	17.6	21.0	16.4	18.2	19.6
270 MHz 30°/11.6 sec[a]	21.4	15.6	22.0	17.0	19.2	20.8
270 MHz 30°/6.6 sec[a]	18.0	14.0	19.2	15.0	17.2	18.0
Average	19.0	15.7	20.7	16.1	18.2	19.5

[a]Pulse angle/ delay between pulses

NMR analyses were carried out at a 30°pulse angle with 6.6 and 11.6 second delays and at a 70° pulse angle with 6.7 second delay between pulses to make certain that relaxation times for different protons do not affect the quantitative results. The variation in DP and copolymer composition under different conditions appear random, indicating the NMR results were devoid of relaxation problems under the conditions of pulse angle and relaxation delay.

The calculation of DP assumed one olefinic end group per molecule, i.e., the copolymer consists of molecules with structures XXIIIa and XXIIIb . The a,b,

c, and d protons individually as well as the total and total plus a' protons in comparison with the e protons were used to calculate DP (Table VII). Each DP value has been corrected to include the olefinic end group, i.e., 1 has been added to the value calculated from the NMR data. The various DP calculated differ in the extent to which both carboxyl and acetamido end groups are counted. The last two calculations are probably the most reliable since both carboxyl and acetamido end groups are counted. They are also less prone to an error in the NMR integral value for any one of the different types of protons since they are based on the sum of all the protons.The last two calculations differ in the extent to which the acetamido end groups are counted. The calculation based on (a + b + c + d) protons under counts the acetamido end groups since the a' protons are excluded. The last calculation which uses a' protons to count acetamido groups overcompensates since it ignores the fact that the acetamido group is partially counted through the d and c protons. The average of the two calculations , DP = 18.9 , is probably a better value than either one of the two. The DP calculated from the NMR data is in excellent agreement with the value of 19.4 obtained from the measurement of $\bar{M}_n$ by vapor pressure osmometry.

We should also note the quantative results for the acetamido NH and carboxyl end group protons. The signal area

Table VIII

Copolymer composition of MeOXO-AA copolymer

NMR Conditions	MeOXO/AA molar Ratio calculated from protons				
	a,b	b,d	b,c	a,c	a,d
300 MHz $70^{o}/6.7$ sec[a]	0.99	0.92	1.20	0.83	0.94
270 MHz $30^{o}/11.6$ sec[a]	1.39	1.09	1.43	0.97	1.09
270 MHz $30^{o}/3.6$ sec[a]	1.29	1.07	1.39	0.93	1.09
Average	1.22	1.03	1.34	0.91	1.04

[a]Pulse angle / delay between pulses

ratio of olefinic protons to the sum of NH and COOH protons should be 3:1 since structures XXIIIa,b have one olefinic end group for all molecules with the second group being either NH or COOH. However, this ratio was found to be about half of the expected value, 1.5:1. The most probable explanation for this result is the presence of traces of moisture in the DMSO-d_6. Water associates with NH and COOH resulting in increases in the signal areas for these protons.

Table VIII shows the copolymer compositions calculated from various comparisons of the a, b, c, and d protons. The most appropriate copolymer composition to be

calculated is the composition of the repeating unit excluding the end groups in order that one can ascertain the extent to which the zwitterion mechanism is responsible for propagation. Thus , the a' and e protons have not been used in the calculations. However, some of the calculations in Table IV are still somewhat in error since signal areas for d and c protons include contributions from the corresponding end groups. This error is less than 5% since it introduces an error only for the molecules containing acetamido end groups. The carboxyl end group contains one each of the AA and MeOXO units while the acetamido end group contains only an MeOXO-derived unit. This error is less than the experimental error inherent in the NMR analytical method and is not considered further. The copolymer composition in the last column, for reasons described above, is probably the most reliable value. The MeOXO-AA ratio is unity within experimental error (at least $\pm$ 10%). The deviation from participation of equimolar amounts of MeOXO and AA in the propagation process is no more than one molecule per ten each of MeOXO and AA.

6.2 Infrared Spectrum

The Infrared spectrum of the copolymer (Figure 8) supports structures XXIIIa and XXIIIb. Two strong absorption bands are observed at 1735 cm^{-1} and 1642 cm^{-1} for the

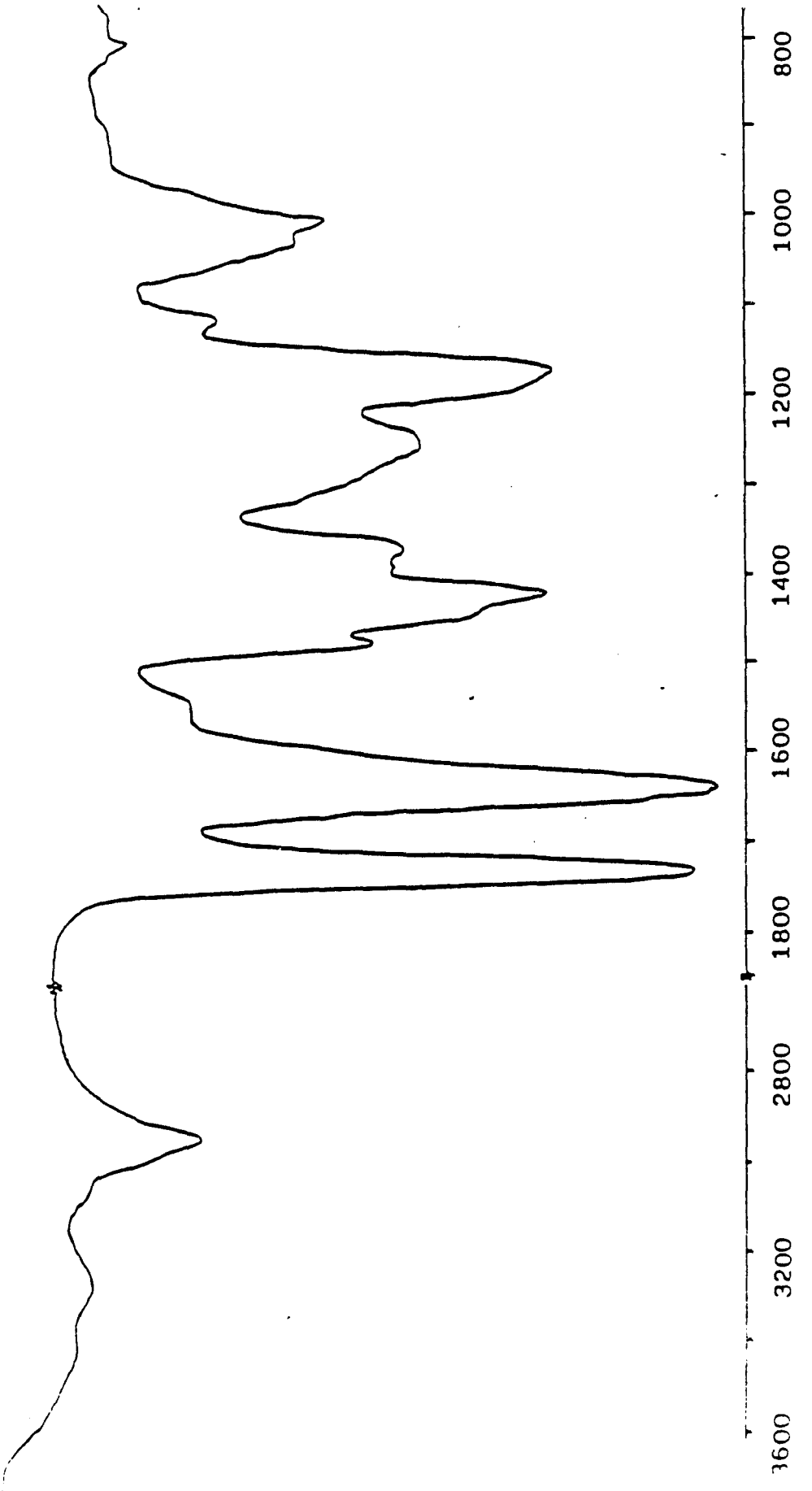


FIGURE 3. Infrared spectrum of MeOXO-AA copolymer (thin mull on NaCl plate).

ester and amide carbonyl groups, respectively, of the repeating unit of the copolymer. Saegusa and coworkers(14) also reported IR data for the presence of amide and ester carbonyls of the copolymer, but no spectrum was provided. Further , the IR data was not discussed in that paper to get information about the end groups of the copolymer.We observed three broad bands in the 3000-3600 cm^{-1} region of the infrared spectrum arising from the end groups of structures XXIIIa and XXIIIb.The band centered near 3050 cm^{-1} , which appears as a shoulder to the sp^3 C-H stretching vibration near 2955 cm^{-1} , is assigned to carboxyl O-H stretching vibration (dimeric carboxyl) of structure XXIIIb and / or the olefinic C-H stretching vibration (45). The absorption band centered at 3290 cm^{-1} is assigned to the N-H stretching vibration of the acetamido end group of structure XXIIIa . The absorption band centered at 3400 cm^{-1} is assigned to the N-H stretching vibration and/or the carboxyl O-H stretching vibration (non- dimeric carboxyl) of structure XXIIIb .

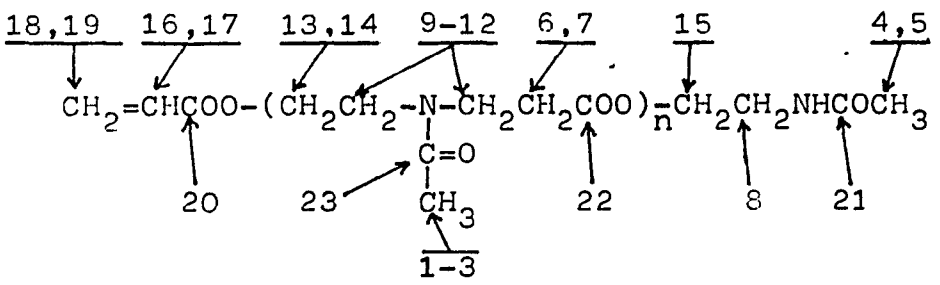
The other IR absorption bands are assigned as follows;

Absorption Band (cm^{-1})	Assignment
2955	C-H Stretching vibration
1422	C-N " "
1172	C-O " "
1375	C-H Bending "
810	CH_2= Wagging vibration of olefinic group

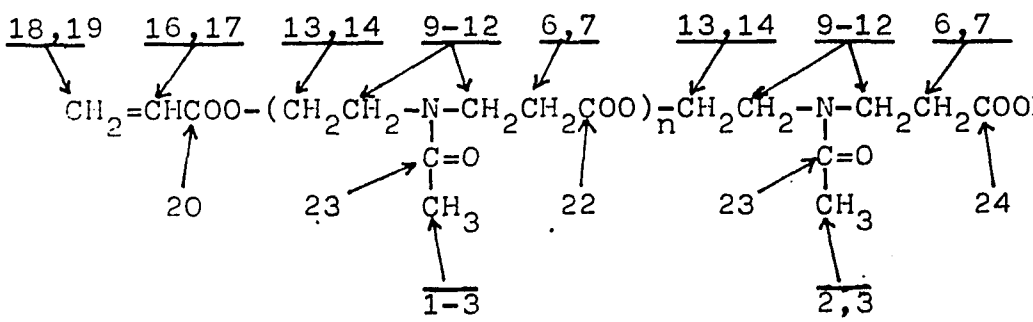
Absorption bands arising from C=C stretching vibration and N-H bending vibration (amide II band) would be expected near the amide carbonyl band at 1642 cm^{-1} . As seen in Figure 8 , the shape of the 1642 cm^{-1} band suggests the possible overlapping of all three absorption bands.

6.3 ^{13}C NMR Spectrum

Figure 9 shows the ^{13}C NMR spectrum of the MeOXO-AA copolymer. The results are consistent with the proposed structures XXIIIa and XXIIIb with the various signals assigned as follows.



XXIIIa



XXIIIb

The chemical shift values of the different signals are listed in Table IX. The assignments of the various

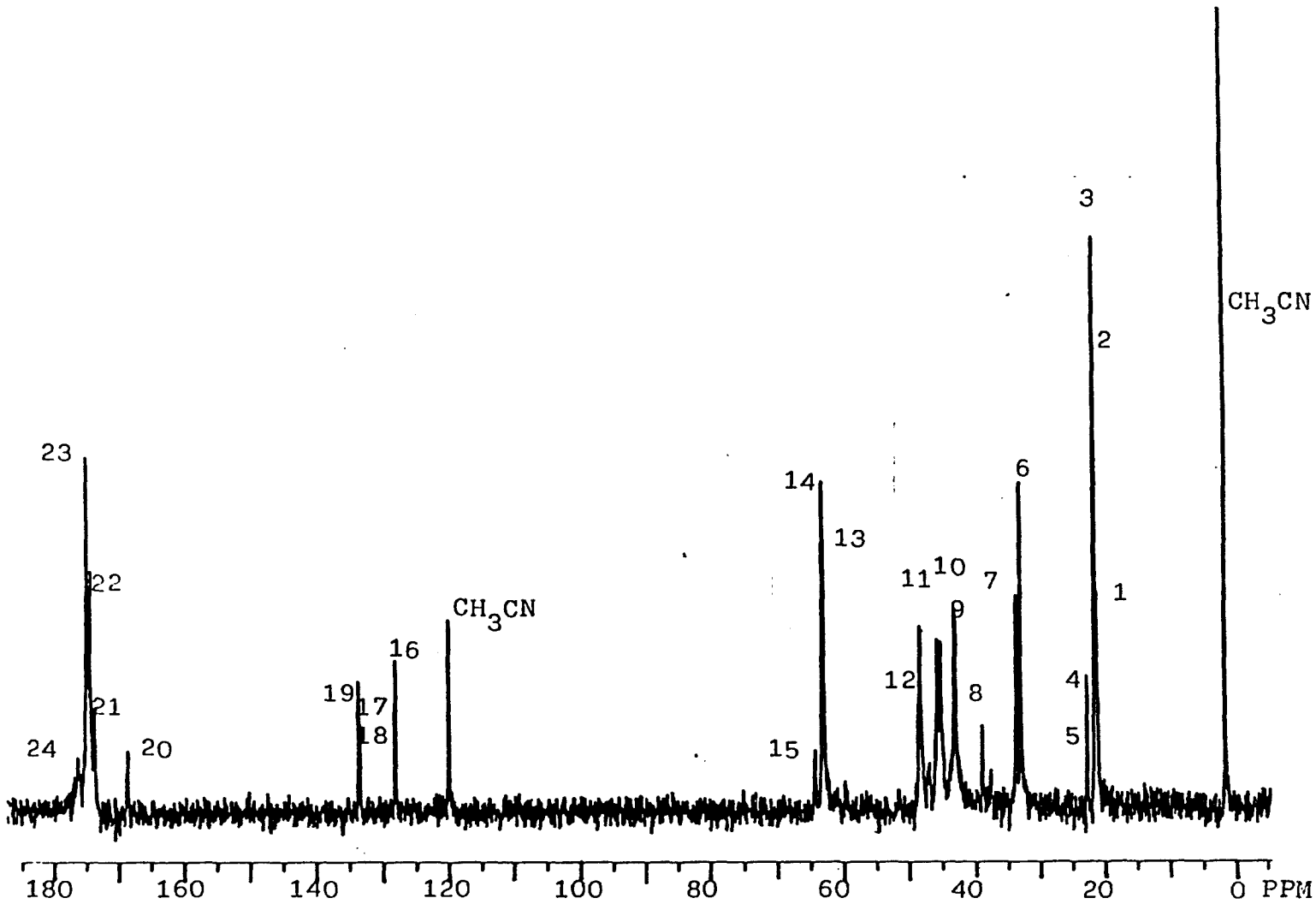


FIGURE 9. 20.1 MHz ^{13}C NMR spectrum of MeOXO-AA copolymer. Conditions: 20% w/v in D_2O; 30° pulse angle ; 33°C; 1.6 sec delay between pulses;80,000 aquisitions; CH_3CN internal standard.

signals were based on the chemical shift values in relationship to those for analogously substituted carbons (45,46). Signals 1-5 were assigned to methyl carbons, signals 6-15 to methylene carbons, signals 16-19 to olefinic carbons, and signals 20-24 to carbonyl carbons. These assignments were also facilitated by the results of single frequency off-resonance (SFOR) decoupling experiments in which we observed the expected splitting of each carbon signal by protons directly attached to the carbon. Within each of the groups of carbon signals, a number of further assignments were relatively easy to make based on chemical shift values. For example, methylene carbons attached to oxygens (signals 13-15) have higher chemical shifts than those attached to amide nitrogens (signals 8-12) which in turn have higher chemical shifts than those attached to ester or acid carbonyls (signals 6,7) . Within some of the groups , specific assignments were made based on a comparison of signal areas and these should be considered as tentative assignments since we have no information on relaxation times for different carbons.Thus, signals 2,3 were assigned to the methyl of the repeating unit while signals 1,4,5 were assigned to the methyls on the acetamido end group and the repeating unit nearest the olefinic end group since the signal areas for the former were much greater than for the latter. Similarly, signals 13,14 were assigned to the repeat unit OCH_2 carbon while signal 15 was assigned to the OCH_2 of the acetamido end

Table IX

^{13}C Chemical Shifts of MeOXO-AA Copolymer

Carbon Number in Structures XXIIIa,b	PPM[a]
1	21.16
2	21.44
3	21.61
4	22.75
5	22.88
6	33.09
7	33.75
8	39.02
9	43.16
10	45.32
11	45.82
12	48.45
13	63.06
14	63.27
15	64.36
16	128.09
17	128.24
18	133.42
19	133.65
20	168.65
21	173.78
22	174.39
23	174.99
24	176.18

[a]Chemical shifts are relative to CH_3CN (methyl carbon 1.70 PPM).

groups; signals 22,23 were assigned to the carbonyls of the repeating unit while signals 20,21,24 were assigned to the carbonyls of various end groups. Two assignments, signals 22 and 23 , are relatively arbitary.The expected difference in chemical shift for ester and amide carbonyls is too small to allow one to differentiate between them with any certainty.

The ^{13}C NMR spectrum shows considerable complexity -- many of the carbons show two signals and some of the signals have significant shoulders. Some of this is evident in Figure 9. It was confirmed when we vieved the spectrum on an expanded scale.Many of the carbons show two signals (each carbon can experience two different NMR environments due to both steric and anisotropic effects.) due to restricted rotation about the C-N amide bond.This is the case for the methyl carbons of the repeating unit (signals 2,3) and the acetamido end group (signals 4,5), each of the four methylene carbons of the repeating unit (signals 6,7,9-14), each of the carbons of the olefinic group (signals 16-19) and most of the carbonyl carbons (signals 20-24).The presence of greater complexity than two signals per carbon is evident since one observes shoulders on signals 7-12,15 , the presence of the small signal between signals 11 and 12 and the presence of more than one shoulder on each of signals 21-23. This complexity in the ^{13}C NMR spectrum is ascribed to the low molecular weight of the MeOXO-AA copolymer. Each of the repeating

units in a molecule of the copolymer is not exactly equivalent . The same type of carbon atom (e.g. the CH_2N carbon) has slightly different chemical shifts depending on its placement relative to the end groups.

7.0 HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

7.1 Fractionation of Copolymer

High performance liquid chromatography was found to be a very useful technique to analyze the MeOXO-AA copolymer. Solubility of the copolymer in solvents such as methanol and water as well as its low molecular weight, fascilitated the use of a μBondapak C_{18} reverse phase column for the HPLC analysis. Due to the presence of amide functional group as part of the copolymer ,a UV detector was used at the wave lenght of 210 nm. The copolymer was found to be stable under the conditions of the HPLC procedure, i.e., the HPLC solvent system did not hydrolyze the the copolymer. This was ascertained by observing the HPLC results to be independent of whether or not the solution of copolymer in the HPLC solvent system was allowed to stand for several hours prior to injection into the HPLC column.

Figure 10 shows the high performance liquid chromatograms of the copolymer and a mixture of authentic samples of AA and MeOXO. It is evident from Figure 10 that the purified copolymer sample does not contain any

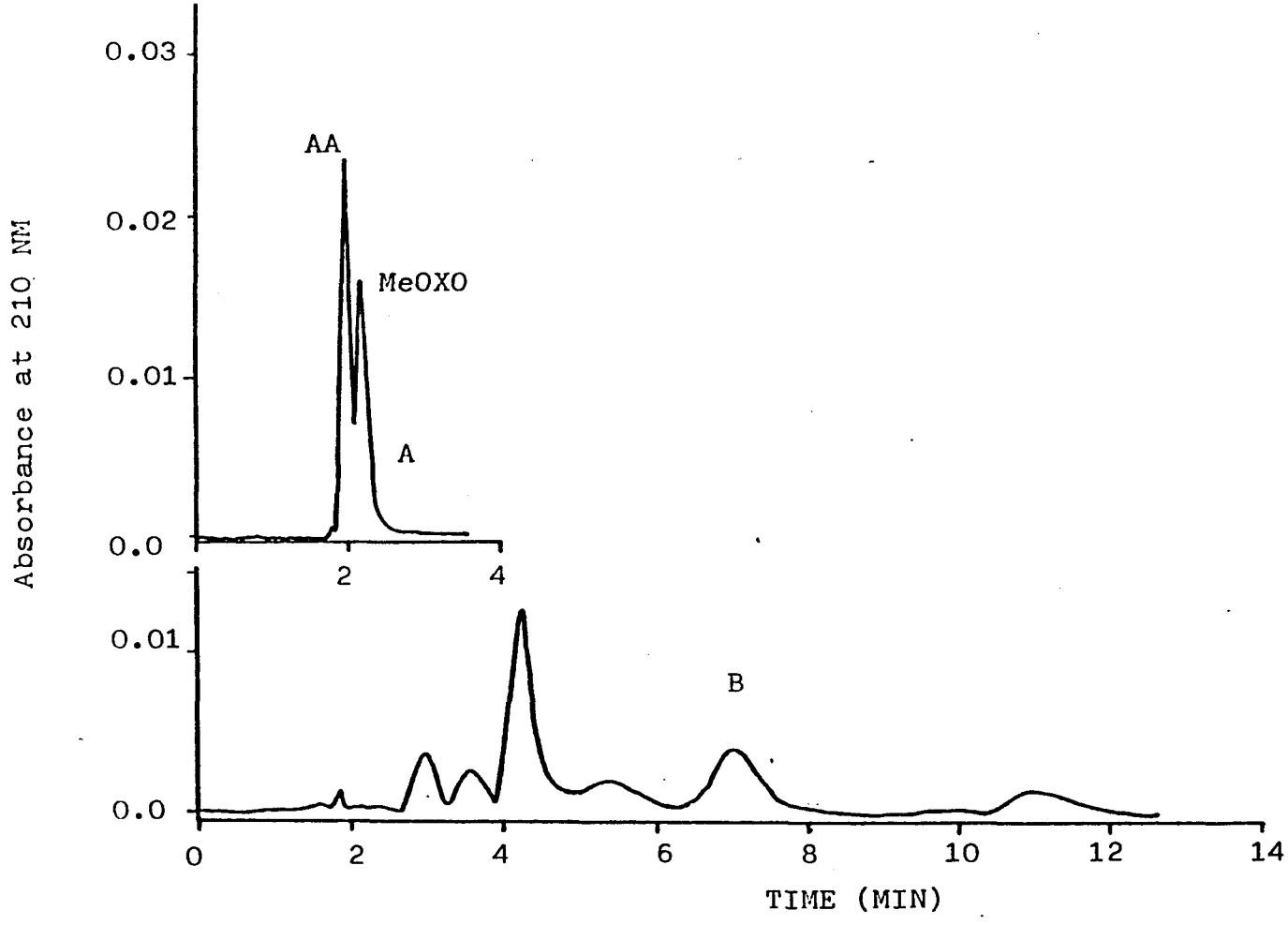


FIGURE 10. A: HPLC of a mixture of AA and MeOXO (authentic compounds) on a μBondapak C_{18} column. Mobile phase: methanol-water-TFA (100:900:0.25).

B. HPLC of MeOXO-AA copolymer under same HPLC conditions.

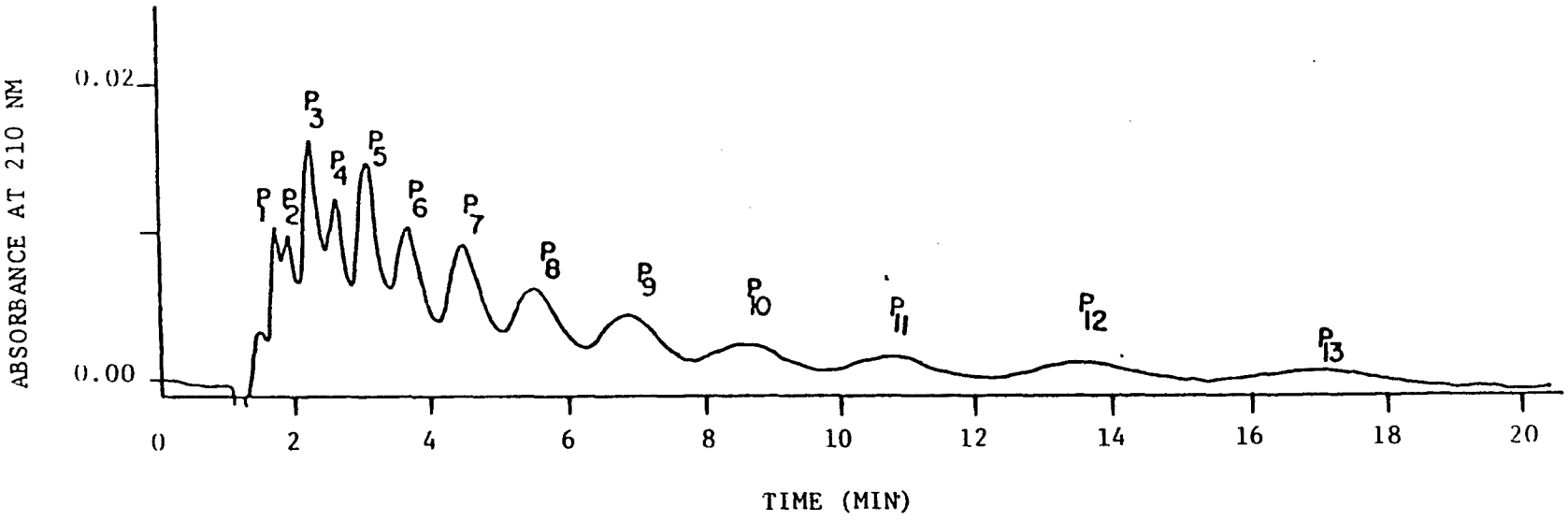


FIGURE 11. HPLC of MeOXO-AA copolymer on a uBondapak C_{18} column. Mobile phase: methanol-water-TFA (350:650:0.8).

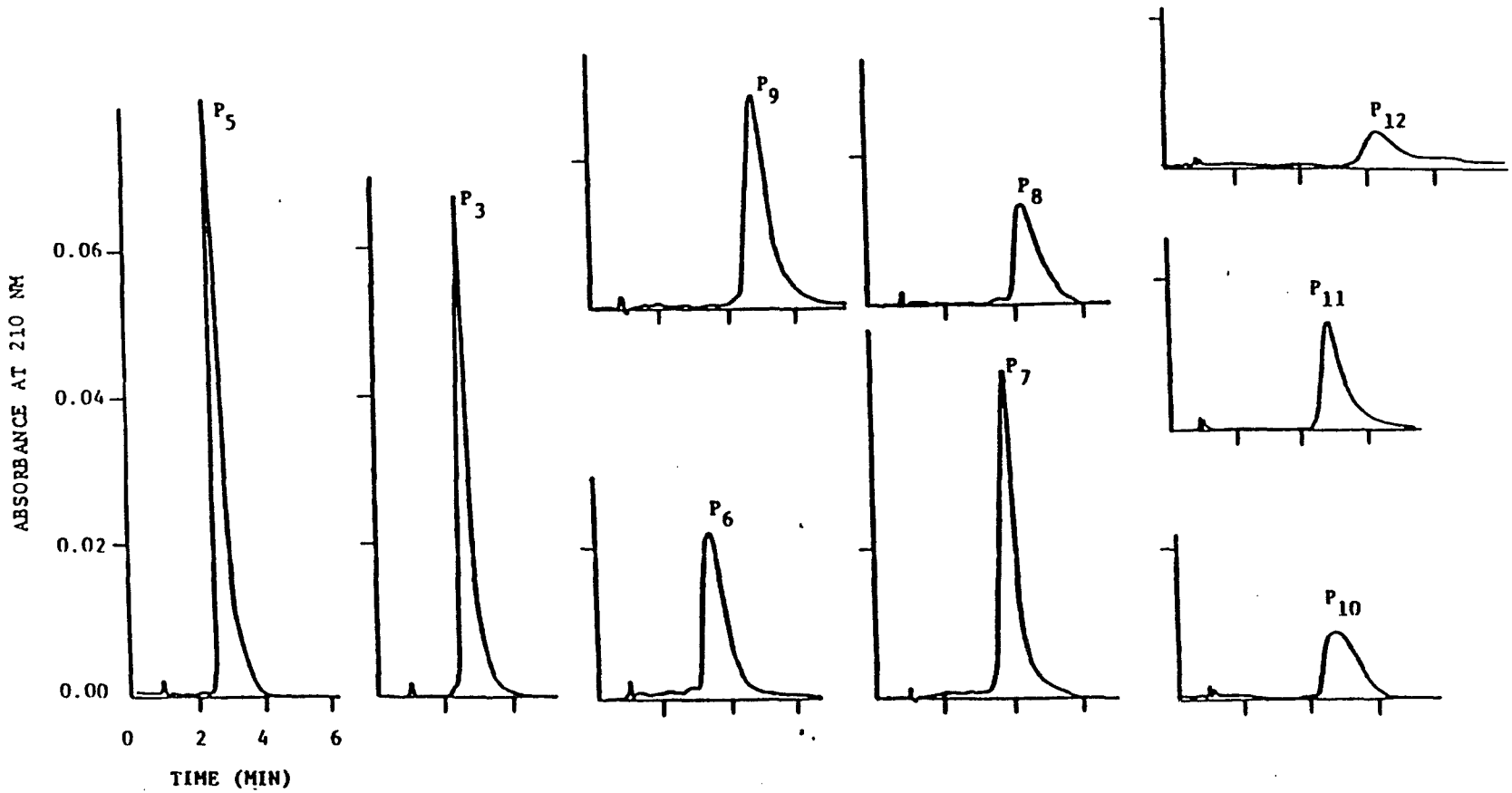


FIGURE 12. HPLC of purified fractions on a μbondapak C_{18} column. Mobile phase: methanol-water-TFA (350:650:0.8) for fractions P_3 through P_9 and methanol-water-TFA (400 600:0.8) for fractions P_{10} through P_{12}. The scale is the same on all plots.

unreacted monomers.This confirms that the olefinic and carboxyl proton and ^{13}C signals in the NMR of the copolymer are due to olefinic and carboxyl end groups and not unreacted acrylic acid.

The copolymer was further analyzed using a different solvent system to examine how many different fractions are present in the copolymer. Figure 11 shows the chromatogram of the copolymer which shows the presence of at least 13 different fractions.The copolymer was fractionated by preparative HPLC using the method described in the experimental section 4.9b. Ten of the 13 fractions were isolated . Fractions P_1, P_2,and P_4 were not isolated since they eluted from the column as mixtures. Analytical HPLC of nine different fractions after fractionation are shown in Figure 12. Considering the complexity of the mixture , the fractionation experiment provided fractions with reasonable purity as evident from the chromatograms shown in figure 12.

7.2 300 MHz Proton NMR Spectra of Isolated Fractions

Each isolated fraction was analyzed by 300 MHz proton NMR spectroscopy. All the fractions showed similar NMR signals for the repeat unit structure of the copolymer and for olefinic end groups.However , there were considerable differences in whether or not signals for acetamido and carboxyl end groups were present.Fractions P_6, P_8 , P_9 and P_{10} showed signals for acetamido end groups but not for carboxyl . Fractions P_3, P_5, P_7, P_{11}, P_{12} ,and P_{13} showed

strong signals for carboxyl end groups and much weaker signals for acetamido end groups.The presence of weaker signals for acetamido end groups in the second group of fractions can be due to the presence of minor amounts of adjascent fractions. For instance, fraction P_5 may contain a minor amount of P_6.Figure 13 shows the proton NMR spectra of P_5 and P_6 as representative examples of the two groups of fractions. Based on NMR results the following structures are proposed for these two fractions.

Fraction P_5:

$$CH_2=CHCOO-(CH_2CH_2-\underset{\underset{CH_3C=O}{|}}{N}-CH_2CH_2COO-)_7CH_2CH_2-\underset{\underset{CH_3C=O}{|}}{N}-CH_2CH_2COOH$$

Fraction P_6:

$$CH_2=CHCOO-(CH_2CH_2-\underset{\underset{CH_3C=O}{|}}{N}-CH_2CH_2COO-)_7CH_2CH_2NHCOCH_3$$

In the NMR spectrum of P_6, the signals d and c shows small details that are not found in d and c of the spectrum of P_5. These additional signals can be considered as due to the two methylene groups $-OCH_2-$ and $-NHCH_2-$ of the acetamido group. Similarly signal b of the spectrum of P_5 has slightly more details due to the $-CH_2-$ next to the -COOH end group.Based on NMR results , the first group of fractions (P_6,P_8,P_9, P_{10}) have structures XXIIIa in

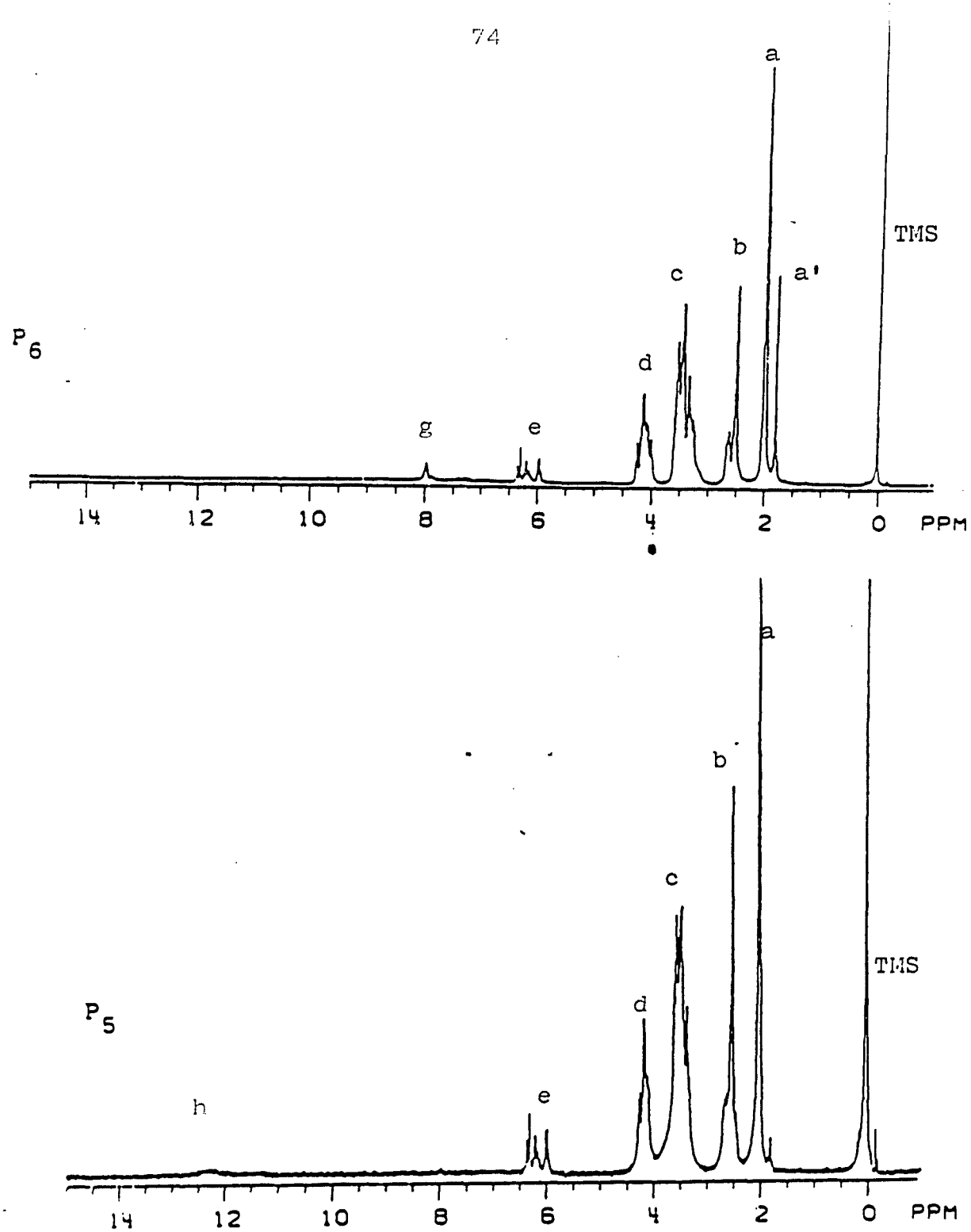


FIGURE 13. 300 MHz FT proton NMR spectra of fractions P_5 and P_6.
P_6: conditions: 1.6% w/v in DMSO-d_6(100%); 50° pulse angle;
4.7 sec. delay between pulses; 25°C; 128 acquisitions.
P_5: Conditions: 1% w/v in DMSO-d_6(100%), 50° pulse angle;
4.7 sec delay between pulses; 25°C; 256 acquisitions.

which the end groups are olefinic and acetamido. The other fractions have mainly structure XXIIIb in which the end groups are olefinic and carboxyl with the presence of minor amounts of structure XXIIIa species.

The copolymer compositions of the repeating unit for the various fractions were calculated from the signal areas for a, b, c, and d protons and are shown in Table X.

Table X

Degree of Polymerization of MeOXO-AA Copolymer Fractions

Fraction	DP	MeOXO/AA
P_3	12.4	0.91
P_5	13.2	0.82
P_6	14.2	0.96
P_7	17.8	0.89
P_8	18.0	0.84
P_9	20.0	0.87
P_{10}	26.6	1.03
P_{11}	33.2	0.88
P_{12}	27.0	0.90
P_{13}	26.2	0.89

The MeOXO-AA ratio is close to unity as found for the unfractionated copolymer sample. DP values for the fractions

were calculated from a comparison of the signal areas for a', a, b, c, d protons to the signal area for e protons. The results indicate that the HPLC separation is based on a combination of factors including molecular weight and end group. For example, the fractions containing acetamido end groups elute from the column in increasing order of molecular weight. For the lower DP fractions, those with acetamido end groups elute after those with carboxyl end groups(compare P_7 and P_8) when the DP is the same for the two types of fractions. However, the reverse is true for the higher DP fractions (P_{10} and P_{12}) . Another anomoly is the reverse dependence of elution time on molecular weight for fractions P_{11}, P_{12}, and P_{13}. These results indicate that some factor other than molecular weight and end group affect the order of elution. Perhaps there are conformational differences (48) between the various fractions which override the other two factors.

Fractions with low and some intermediate DP values are absent from the results shown in Table X. The missing low DP fractions probably comprise the unisolated fractions P_1, P_2, and P_4 as well as the ether solution which results when the MeOXO-AA copolymer is precipitated from the reaction mixture. The absence of some intermediate DP fractions may indicate that some of the isolated fractions contain mixtures. For example, P_{10} may contain molecules with DP less than 26.6 and greater than 26.6.

8.0 HYDROLYSIS OF COPOLYMER

Further proof for the proposed structures XXIIIa and XXIIIb was obtained by analysis of the products from alkaline hydrolysis of unfractionated copolymer. Alkaline hydrolysis of structure XXIIIb would yield N-(2-hydroxyethyl) -β-alanine and acetic acid from the repeating unit structure and acrylic acid from the olefinic end group.

$$\text{XXIIIb} \xrightarrow[2.\ H_3O^+]{1.\ OH^-} (n+1)\ \underset{\text{(XXIV)}}{HOCH_2CH_2NHCH_2CH_2COOH} + (n+1)\ \underset{\text{(XXV)}}{CH_3COOH} + \underset{\text{(XXVI)}}{CH_2{=}CHCOOH} \qquad (31)$$

$$\text{XXIIIa} \xrightarrow[2.\ H_3O^+]{1.\ OH^-} n\ HOCH_2CH_2NHCH_2CH_2COOH + (n+1)\ CH_3COOH + CH_2{=}CHCOOH + \underset{\text{(XXVII)}}{HOCH_2CH_2NH_2} \qquad (32)$$

Hydrolysis of structure XXIIIa would yield XXIV, XXV, XXVI and ethanolamine from the acetamido end group.

Presence of homosequence of either monomer would result in additional hydrolysis products XXVIII and XXIX respectively.

Homosequence of acrylic acid;

$$-(CH_2CH_2\underset{\underset{CH_3C=O}{|}}{N}CH_2CH_2COO-)_n(CH_2CH_2COO-)_m \xrightarrow[2.\ H_3O^+]{1.\ OH^-}$$

$$n\ \underset{\text{(XXVIII)}}{HOCH_2CH_2COOH} + \text{XXV} + \text{XXIV} \qquad (33)$$

Homosequence of MeOXO;

$$-(CH_2CH_2\text{-}N(CH_3C{=}O)\text{-})_m(CH_2CH_2\text{-}N(CH_3C{=}O)\text{-}CH_2CH_2COO\text{-})_n \xrightarrow[2.\ H_3O^+]{1.\ OH^-}$$

$$HO(CH_2CH_2\text{-}NH)_{m+1}CH_2CH_2COOH + XXV$$

(XXIX) (34)

Although Saegusa and coworkers (14) reported evidence from hydrolysis experiments to support the structure, the results were less than conclusive since no attempt was made to isolate any of the possible hydrolysis products nor to identify those originating from the end groups.They provided evidence for the presence of XXIV and XXVI among the hydrolysis products by comparing the proton NMR of the hydrolysis mixture with that of a mixture of authentic compounds of XXIV and XXV.

Figure 14 shows the analytical HPLC of the hydrolyzed MeOXO-AA copolymer after acidification with HCl . The three peaks were attributed to N-(2-hydroxyethyl) -β-alanine, acetic acid, and acrylicacid respectively, in order of increasing retention time by injecting authentic samples of each compound.Although acrylic acid comes from the hydrolysis of the end group , the observed relatively large area for that peak is as a result of the large extinction coefficient of acrylic acid.The extinction coefficients of acetic acid and acrylic acid at 210 nm were determined and found to be 35 and 2621 respectively.The ratio of acrylic acid to acetic acid in

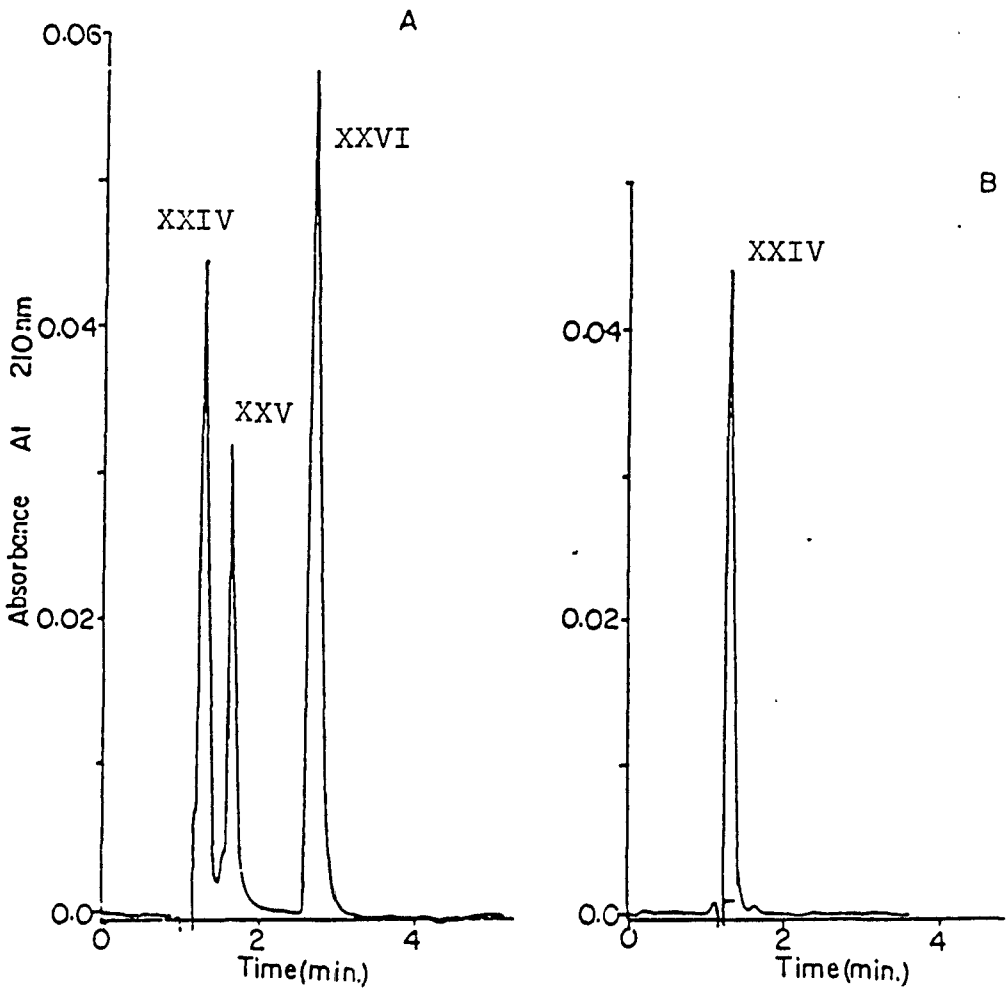


FIGURE 14. A: HPLC of MeOXO-AA copolymer hydrolyzate on a μBondapak C_{18} column using water-TFA (500:0.3) as the mobile phase.
B: HPLC of an authentic sample of N-(2-hydroxyethyl)-β-alanine under the same HPLC conditions.

the hydrolysis products when calculated based on these results was 1:19. This value is higher than the expected value (1:9) obtained from NMR data and molecular weight data. Two possible reasons can be mentioned for this difference.

i). The area for the acetic acid peak was difficult to be determined accurately due to the poor base line separation. Attempt to find a solvent system to get a better separation was not successful.

ii). Since the hydrolysis was done at 100°C , the product acrylic acid may have undergone other side reactions such as polymerization which makes the area of AA smaller than the real value.

We isolated N-(2-hydroxyethyl)-β-alanine in pure form from the hydrolysis products. The proton NMR spectra (Figure 15) and mp were identical with those of the authentic compound.

Proton NMR of N-(2-hydroxyethyl)-β-alanine;

$$HOCH_2CH_2NHCH_2CH_2COOH$$

3.86 3.24 2.58

(Chemical shift in PPM with respect to internal TMS, signals for OH, NH and COOH protons appear as one signal at 4.7 PPM since the NMR was recorded in D_2O.)

The presence of acrylic acid and acetic acid among the hydrolysis products was shown by gas chromatography (see section 4.5) and analytical HPLC (Figure 16).

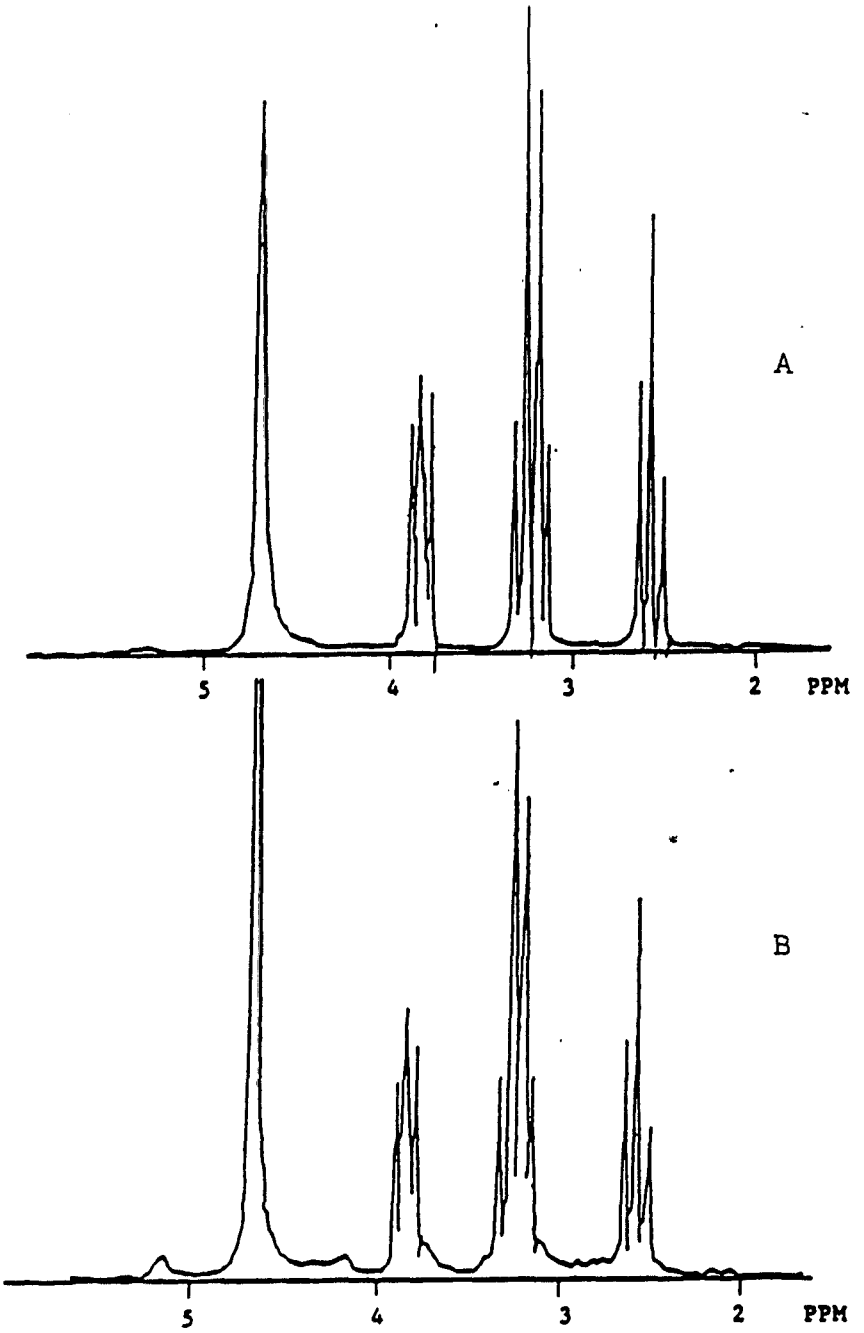


FIGURE 15. 100 MHz proton NMR of
A: N-(2-hydroxyethyl)-β-alanine (authentic compound) in D_2O (8% w/v) at room temperature.

B: Sample isolated from hydrolyzed MeOXO-AA copolymer in D_2O (6% w/v) at room temperature. Internal standard DSS.

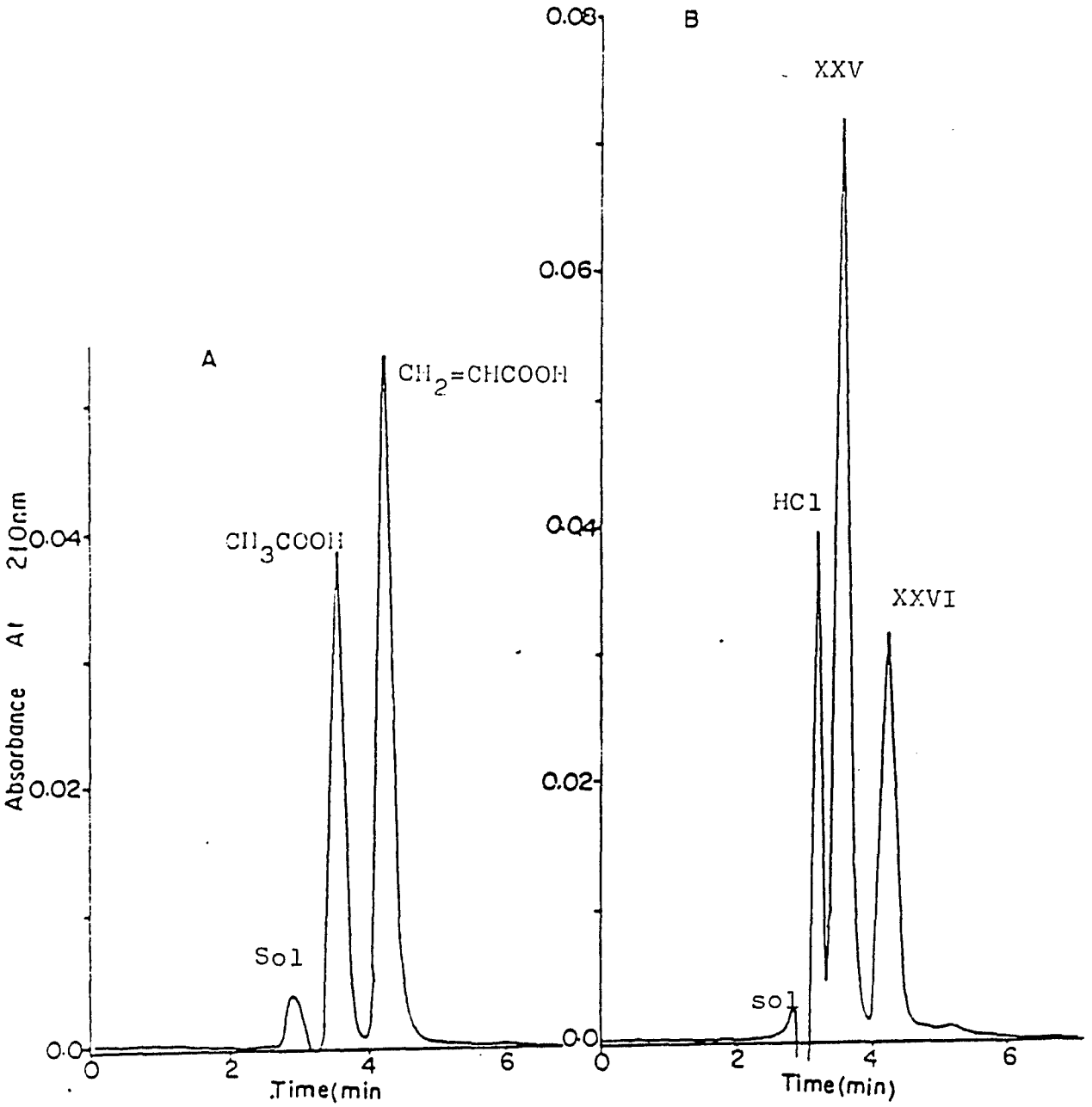
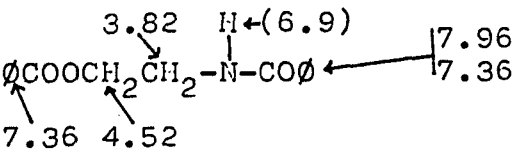


FIGURE 16. A: HPLC of a mixture of acetic acid and acrylic acid on a μBondapak C_{18} column using water-TFA (500:0.3) as the mobile phase.
B: HPLC of the eluent from the cation exchange resin column under the same HPLC conditions.

Attempted isolation of ethanolamine from the hydrolysis products was not successful mainly because of the smaller amount present.Therefore this material was converted to its dibenzoyl derivative directly from the hydrolysis mixture and purified by HPLC.Comparison of the proton NMR spectrum of this compound with that of the authentic compound (Figure 18) clearly indicated that the isolated product is infact the dibenzoate of ethanolamine.

Proton NMR of dibenzoate of ethanolamine;



(Chemical shift in PPM from internal TMS.)

The presence of three multiplets for the protons of the two phenyl groups is as a result of the restricted rotation about the C-N bond. In the benzoylation procedure , a second (minor) product was obtained along with the dibenzoate of ethanolamine.This is the component with a retention time slightly below 7 minutes in the HPLC in Figure 17. (The component with a 2 minute retention time is the solvent.) The minor product was separated by HPLC and its proton NMR observed.The proton NMR showed complex absorptions in the aromatic region 7.1-7.9 PPM and broad aliphatic absorptions at 3.6, 3.8, and 4.4 PPM with an overall aromatic:aliphatic proton ratio of about 2.1:1. The most likely possibility for this product is the tribenzoate derivative of N-(2-hydroxyethyl)-β-alanine

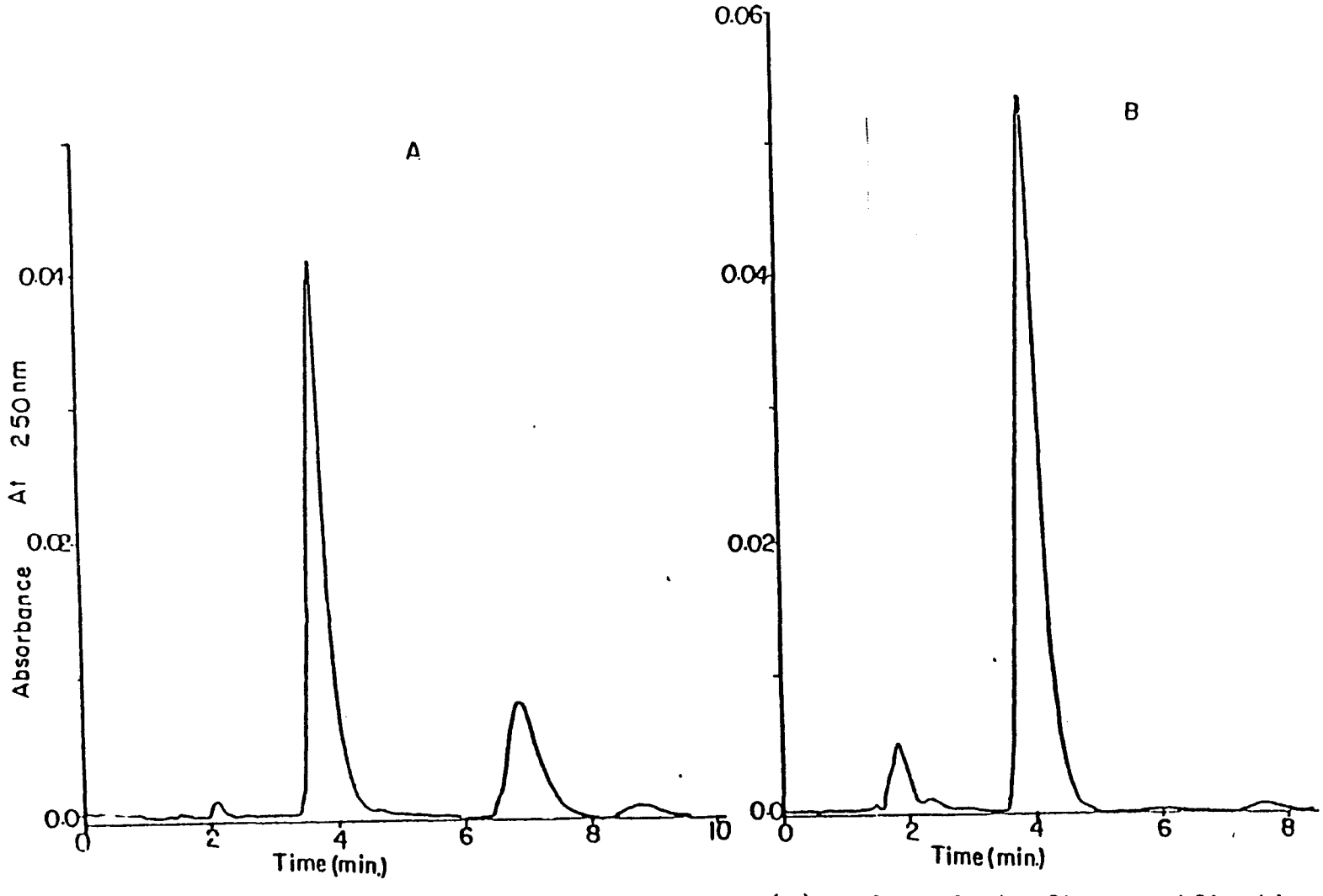


FIGURE 17. HPLC of crude benzoylated product (A) and product after purification (B). Stationary phase: μBondapak C_{18} column. Mobile phase: methanol-water-TFA (550:450:0.6).

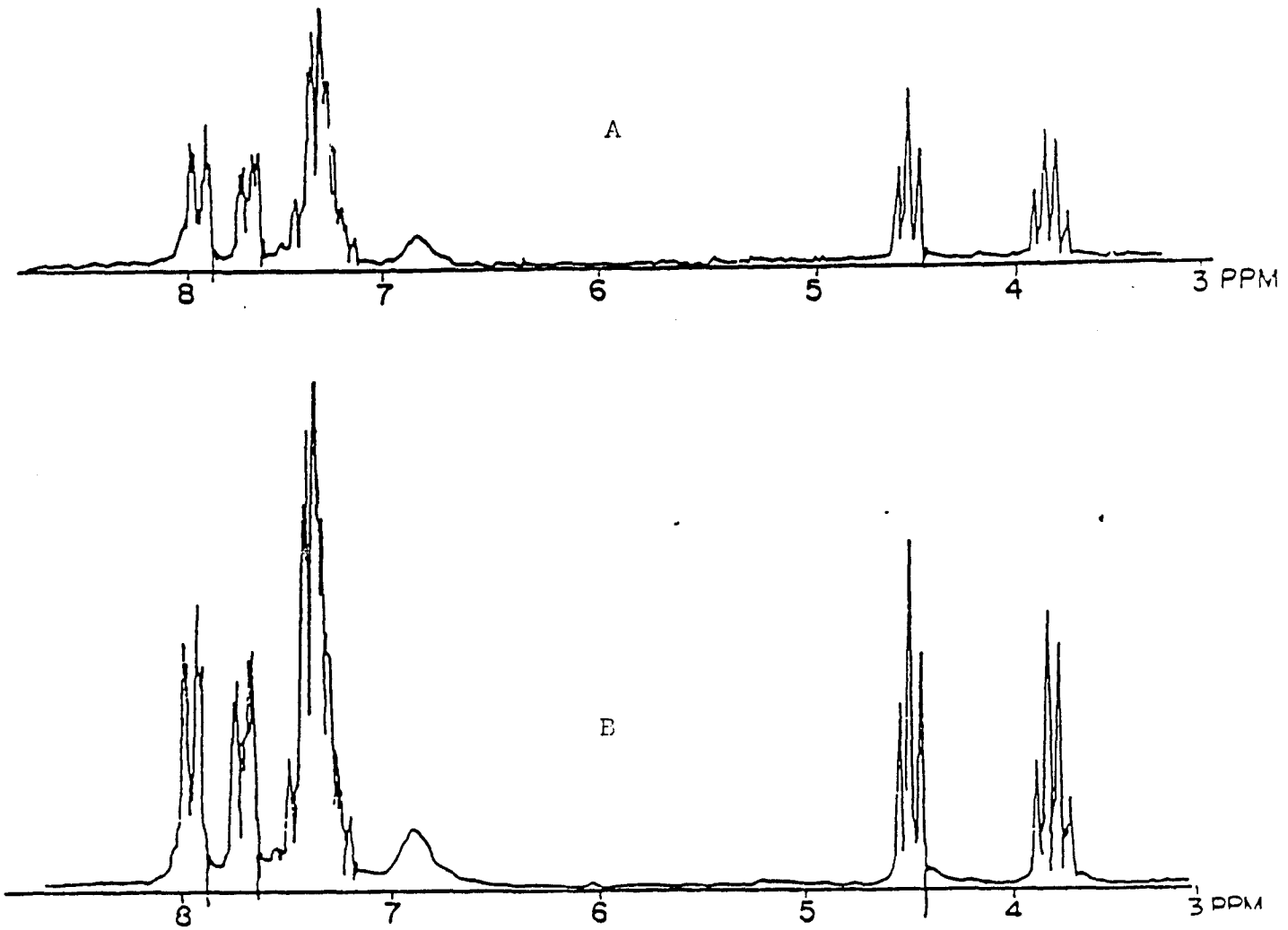


FIGURE 18. 100 MHz proton NMR of

A: $\emptyset COOCH_2CH_2NHCO\emptyset$ (authentic sample) in $CDCl_3$ (8% w/v) at room temperature.

B: Compound isolated after benzoylation of hydrolyzed MeOXO-AA copolymer in $CDCl_3$ (4% w/v) at room temperature.

Internal standard TMS.

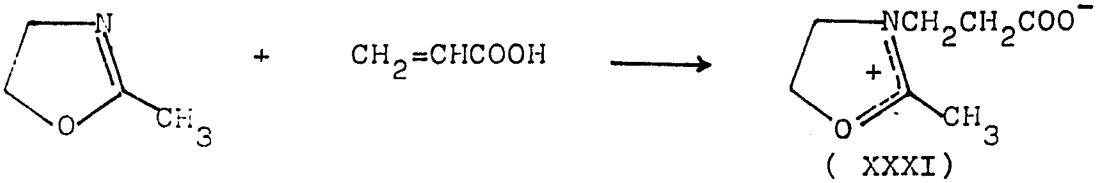
which would have an aromatic:aliphatic proton ratio of 1.9:1 and complex or broad patterns for both aromatic and aliphatic regions. Benzoate dervative of XXVIII and XXIX are not likely possibilities.The dibenzoate derivative of XXVIII would have a simple absorption pattern in the aliphatic region and a aromatic:aliphatic proton ratio of 2.5:1. The tetrabenzoate of XXIX (with m=1) would have the required complex aliphatic and aromatic absorption but an aromatic:aliphatic proton ratio of only 1.67:1.

In summary., the hydrolysis experiments have shown the presence of the expected hydrolysis products from structures XXIIIa and XXIIIb. No experimental evidence has been found for significant amounts of homosequences of either MeOXO or AA.

9.0 DIRECT PROTON NMR ANALYSIS OF REACTION MIXTURE

9.1 2-Methyl-2-Oxazoline and Acrylic Acid

The main objective of the direct NMR analysis experiment was to find evidence for the formation of zenetic zwitterion intermediates such as XXXI during the copolymerization reaction.

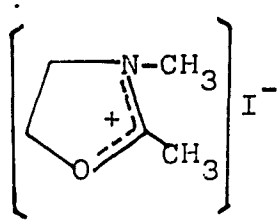


(XXXI)

The large difference in chemical shifts for various

protons of the two monomers (see Table II) enables us to differentiate these signals even when the NMR spectrum of a mixture of the two monomers recorded.If genetic zwitterion intermediates are formed , the NMR signal of the methyl group attached to the oxazolinium ring of the genetic zwitterion should have a higher chemical shift (lower field) than that of the monomer MeOXO and the copolymer methyl groups.In order to find the chemical shift of such a methyl group, the model compound N-methyl-2-methyl-2-oxazolinium iodide (XXXII) was prepared.The 100 MHz proton NMR data of the model compound XXXII are shown below

Chemical shift (PPM)	Assignment
2.32	$C-CH_3$
3.32	$N-CH_3$
4.16	$N-CH_2$
4.91	$O-CH_2$



(XXXII)

(Spectra taken at 100 MHz in CD_3CN with TMS as the internal standard.)

The methyl group attached to the oxazolinium ring of the model compound appears at 2.43 PPM. Therefore it is reasonable to expect a signal around 2.43 PPM for the reaction mixture if genetic zwitterion intermediates are formed during the copolymerization reaction.Figure 19A

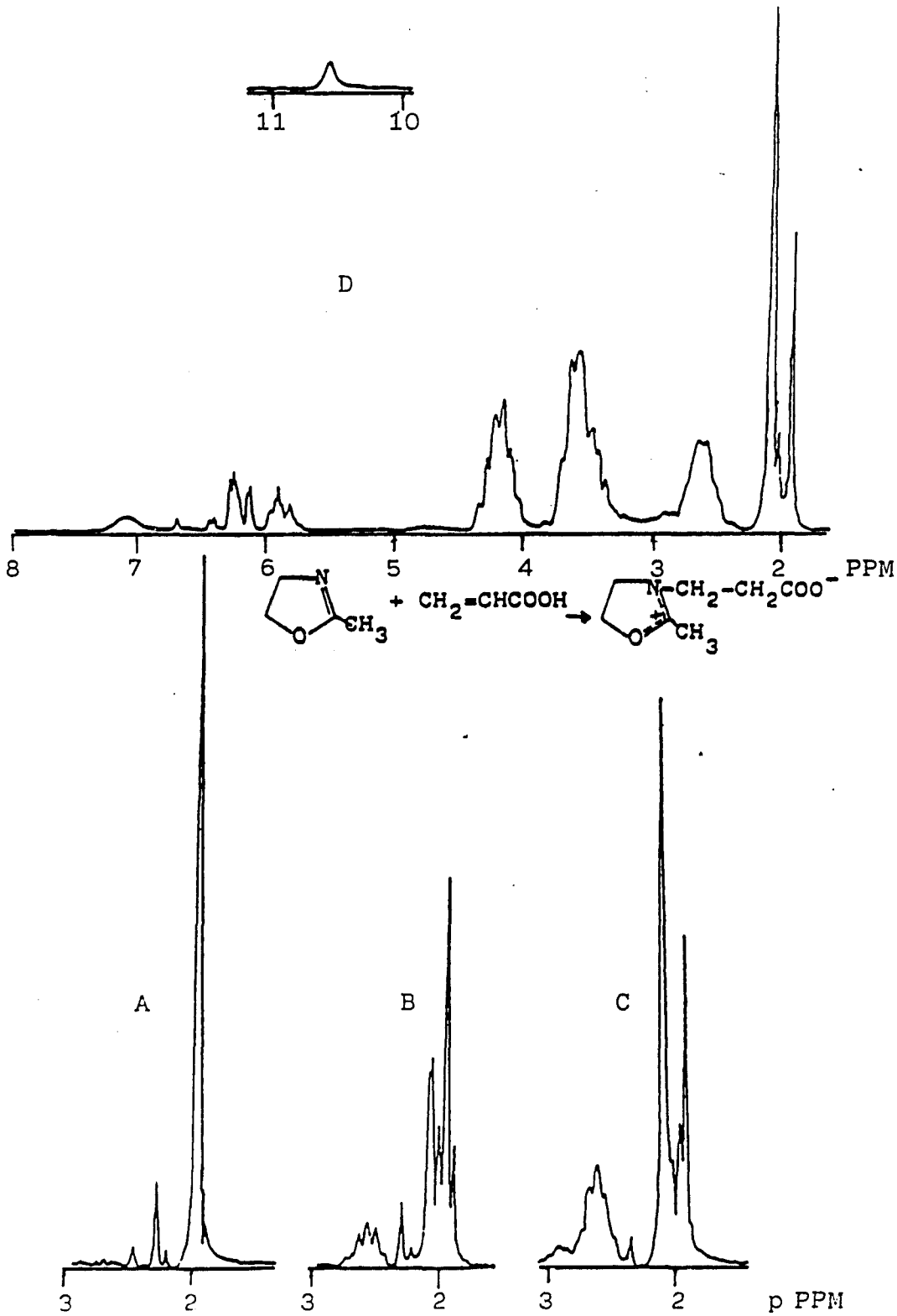


FIGURE 19. 100 MHz proton NMR spectrum of an equimolar mixture of AA and MeOXO in CD_3CN. A: 3 hours after mixing. B: 2 hours at 60°C. C: 15 hours at 60°C. D: Complete spectrum after 40 hours at 60°C.

shows the 1.5-3 PPM region of the 100 MHz proton NMR spectrum of an equimolar mixture of MeOXO and AA in acetonitrile at room temperature (25°C) .The signal at 1.98 PPM is assigned for the methyl group of the monomer and the new signal at 2.32 PPM can be assigned to the methyl group of the genetic zwitterion intermediate. Figure 19B and 19C shows the same region NMR spectrum of the reaction mixture after two hours and 15 hours of reaction time at 60°C , respectively. Figure 19D shows the complete spectrum of the reaction mixture after 40 hours of reaction time at 60°C. As the reaction proceeds, the appearance of signals at 2.06 PPM due to the methyl group of copolymer and at 1.90 PPM due to the methyl group of $-NHCOCH_3$ can be observed. The multiplet at 2.50 PPM is assigned to the methylene protons of the $-CH_2CO-$ group of copolymer.The intensity of the signal at 2.32 PPM decreased gradually while the intensities of the signals at 2.06, 1.90, 2.5 PPM increased with the progress of the reaction. Figure 19D which shows the complete spectrum of the reaction mixture after 40 hours of reaction time at 60°C, clearly indicates the complete disappearance of the signal at 2.32 PPM.Further,the spectrum did not show any appreciable changes even after very long reaction times (3 days at 60°C) . The disappearance of the signal at 2.32 PPM may indicate that all the active polymer chains undergo some form of termination .The other important

results of this experiment can be summarized as follows.

i). A broad signal at 7.12 PPM started to appear in the spectrum almost simultaneously with the appearance of the signal at 1.9 PPM. The area ratio of these signals was approximately 1:3. Therefore, this broad signal can be assigned to the NH proton of the acetamido end group $-NHCOCH_3$. The high field observed for this signal compared to the position of the NH at 7.95 PPM of the isolated copolymer is considered due to the medium effect resulting from the use of two different solvents (7.12 PPM in CD_3CN and 7.95 PPM in DMSO-d_6). The broad signal started to appear in the spectrum of the reaction mixture after about two hours of reaction time at 60°C. The appearance of the NH proton signal early in the reaction is an indication of the early termination of growing polymer chains to give acetamido type end groups.

ii). The assignment of the 2.32 PPM signal in Figure 19A to the genetic zwitterion appears definitive. Other possibilities for this downfield shifted $C-CH_3$ signal are the $C-CH_3$ of the protonated MeOXO and the $C-CH_3$ of macrozwitterion.The former is excluded since no NH type of signal was observed in the spectrum of the reaction mixture three hours after mixing.The latter is excluded since no signals characteristic of the repeating unit are present in Figure 19A.

iii). The position of the carboxylic proton signal

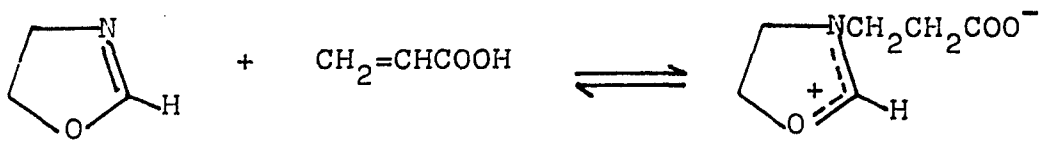
changed with the reaction time from an initial value of 12.63 PPM to 10.6 PPM after 40 hours of reaction time. This may be due to the change in the concentration of AA as the reaction proceeds.

iv). Even after a very long reaction time (3 days at 60°C),the NMR spectrum of the reaction mixture showed the presence of carboxylic proton signal as well as the olefinic proton signals (multiplet at 6.0 PPM).Further, the area ratio for carboxylic proton signal to olefinic protons signals was 1:4.8 after 40 hours of reaction time which should be 1:3 if these signals are due to only unreacted monomer AA.

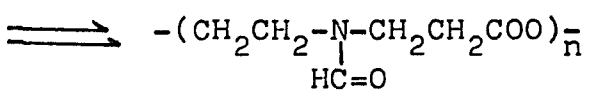
The ability to monitor the polymerization reaction by NMR enabled us to study the copolymerization under low temperature conditions. In another experiment , equimolar amounts of MeOXO and AA were mixed under liquid nitrogen cooling and the NMR spectrum of the reaction mixture recorded after storing 10 hours in liquid nitrogen. NMR spectrum showed signals for protons of the two monomers and no sign of any reaction between the two monomers under these conditions.However, when the monomer mixture was left at room temperature for several hours the appearance of signals as described previously indicated the start of the polymerization.A similar experiment was done at 0°C and no appreciable reaction was observed at this temperature also. Genetic zwitterion formation at reasonable rates appears to occur only at ambient or high temperatures.

9.2 2-Oxazoline and Acrylic Acid

Similarly , the direct NMR analysis was used to monitor the reaction of 2-oxazoline and acrylic acid monomer system. The possible genetic zwitterion intermediate (XXXIV) in this case has a proton attached to the positively charged carbon 2 of the oxazolinium ring. Hence, the NMR signal for this proton should appear at a significantly lower field relative to the proton of the free monomer.



(XXXIV)



(copolymer)

Figure 20A shows the NMR spectrum of (6.5-8.5 PPM region) an equimolar mixture of OXO and AA in CD_3CN recorded at room temperature two hours after mixing. The signal at 7.04 PPM is due to the proton attached to the carbon 2 of the free monomer OXO. The new signal at 8.20 PPM can be assigned to the same proton of the genetic zwitterion intermediate. Figure 20B and 20C show the NMR spectra of the reaction mixture after 1½ hours and 44 hours reaction

time at 60°C , respectively. As the reaction proceeds the appearance of new NMR signals at 8.07 PPM and 7.96 PPM for formamido proton (-NHCO, appears as two signals due to C-N restricted rotation) of copolymer can be seen. Also of significant importance is the formation of a broad signal at 7.18 PPM (see Figure 19C) similar to that observed in the case of MeOXO-AA system. This signal can be assigned to the NH proton of the possible formamido end group.-NHCHO. Figure 20D shows the complete spectrum of the reaction mixture after a very long reaction time (3 days at 60°C) The spectrum clearly shows the absence of any unreacted OXO in the reaction mixture (absence of NMR signal at 7.04 PPM), and the presence of olefinic (6.1 PPM) and carboxylic protons (10.5 PPM) signals. In another experiment, OXO was used in excess (OXO:AA molar ratio , 3:2) and the NMR spectrum of this reaction mixture after 90 hours of reaction time is shown in Figure 20E. The presence of unreacted OXO in the reaction mixture can be clearly seen by the signal at 7.04 PPM. Even under these conditions, NMR signals due to both olefinic and carboxylic protons can still be seen. Use of excess OXO ensures the complete reaction of acrylic acid present in the reaction mixture. If the observed signals are due to unreacted AA , the area ratio for olefinic to carboxylic proton signals should be 3:1. However, the observed value of this ratio is 12:1 . Therefore , the observed signals

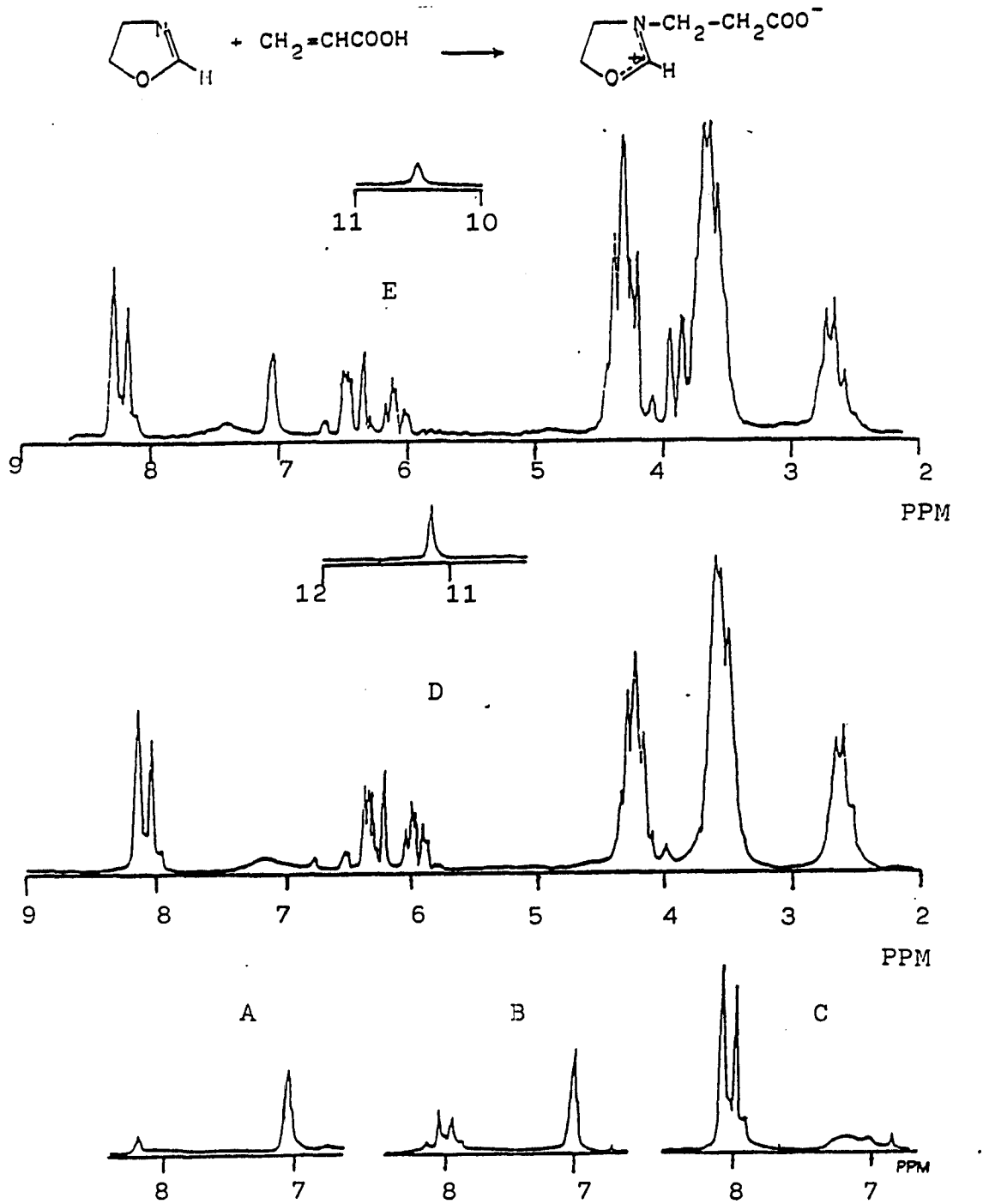


FIGURE 20. 100 MHz proton NMR spectrum of equimolar mixture of AA and OXO in CD_3CN . A: 2 hours after mixing B: 1.5 hours at 60°C. C: 44 hours at 60°C. D: Complete spectrum after 3 days at 60°C. E: Mixture of OXO-AA (molar ratio 3:2) after 90 hours at 60°C.

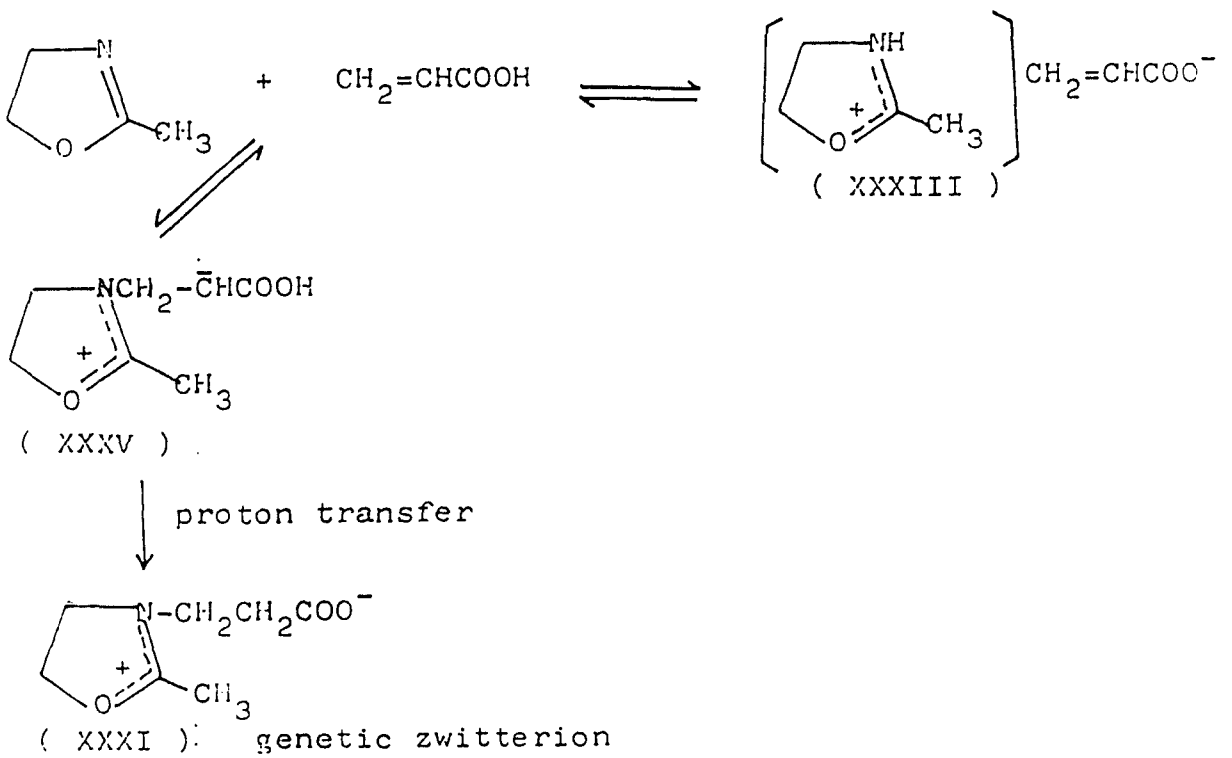
for olefinic and carboxylic protons may come from part of the polymer chain (most probably from olefinic and carboxylic end groups) or from some other product formed during the polymerization reaction.

From the results of the direct NMR analysis experiments , it appears that both OXO-AA and MeOXO-AA monomer systems behave in a similar manner. Reactions responsible for termination of growing macrozwitterions in the polymerization of OXO-AA system can be considered to involve the reaction of a growing macrozwitterion with quaternized acrylate salt of OXO or monomer acrylic acid yielding polymer chains with olefinic and formamido , and olefinic and carboxylic end groups respectively.Besides the experimental evidence obtained to show the formation of zenetic zwitterions , these experiments have provided information about the termination reactions involved.

PROPOSED POLYMERIZATION MECHANISM

A summary of the experimental results is useful before presenting the proposed polymerization mechanism. The copolymer composition has been estabilished as 1:1 by proton NMR. Proton and ^{13}C NMR have identified the end groups as olefin , carboxyl, and acetamido. Infrared spectroscopy supports this conclusion. Hydrolysis experiments corroborate both the copolymer composition and identity of end groups. Direct proton NMR analysis of the reaction mixture gave evidence for the genetic zwitterion. HPLC showed that the copolymer product consists of different-sized molecules and not all molecules have the same two end groups.The following reaction mechanism is proposed to describe the MeOXO-AA polymerization.

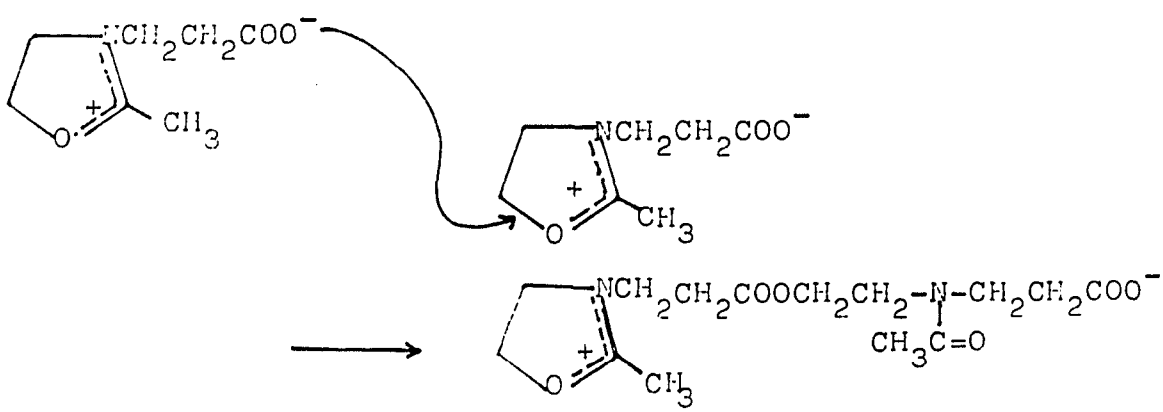
Initiation



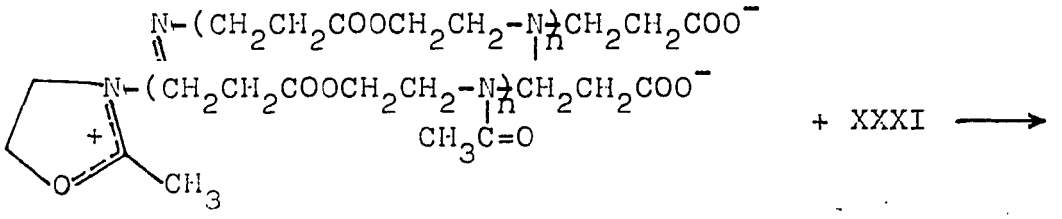
The initiation involves the reaction of MeOXO with AA to form the adduct XXXV which by a proton transfer reaction forms the genetic zwitterion intermediate XXXI. The evidence for the formation of genetic zwitterion type intermediate is obtained in the direct NMR analysis experiment. The formation of quaternized oxazolinium acrylate salt XXXIII can be considered as a competing reaction with the reaction forming genetic zwitterions. There are no experimental evidence to consider the formation of salt XXXIII soon after the monomers are mixed at room temperature . However, as the reaction mixture is heated at 60°C , the observed NMR signals for acetamido type end group indicates the reaction of zwitterions with the quaternized salt XXXIII to undergo termination.

Propagation

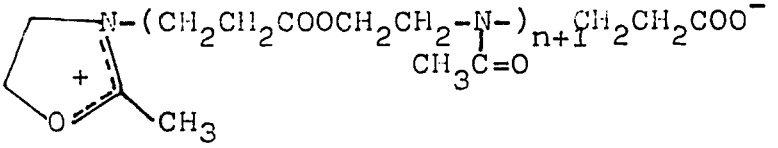
The propagation can be considered to involve the reaction of genetic zwitterion XXXI with itself



and the resulting larger sized zwitterions XXXVI.



(XXXVI)

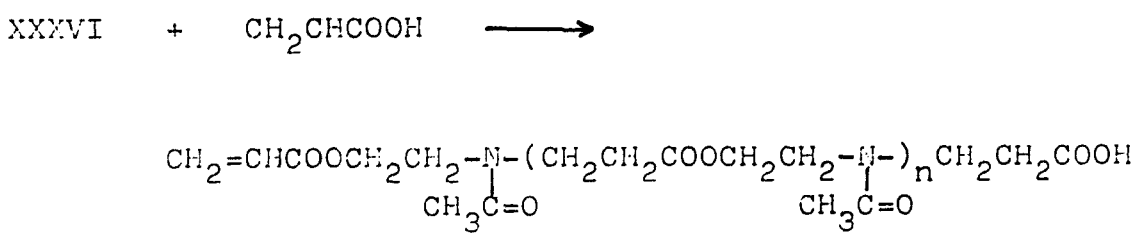


The propagation by the reaction between two macrozwitterions is also possible.

Termination

Two reactions can be considered responsible for the termination of growing polymer chains.

i). Termination involving the reaction of a growing macrozwitterion with monomer acrylic acid to give olefinic and carboxylic end groups.



ii). Termination involving the reaction of a growing macrozwitterion with the quaternized oxazolinium acrylate salt XXXIII to give olefinic and acetamido end groups

XXXVI + XXXIII ⟶

$$CH_2{=}CHCOOCH_2CH_2{-}\underset{\underset{CH_3C{=}O}{|}}{N}{-}(CH_2CH_2COOCH_2CH_2{-}\underset{\underset{CH_3C{=}O}{|}}{N}\overset{+}{)}_n CH_2CH_2COOCH_2CH_2NHCOCH_3$$

The proposed polymerization mechanism is consistent with the isolation of various hydrolysis products and the spectroscopic data for the presence of acetamido , olefinic and carboxylic end groups. Early termination of growing polymer chains by reacting with monomer acrylic acid and with quaternized oxazolinium acrylate salt explains the difficulty to obtain high molecular weight copolymers in the zwitterion polymerization of MeOXO-AA monomer system.

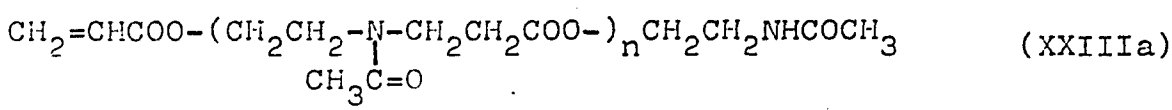
11.0 CONCLUSIONS

2-Methyl-2-oxazoline and acrylic acid undergo polymerization without any added initiator or catalyst in solution or in bulk to give low molecular weight copolymers. Vapor pressure osmometry showed the number average molecular weight to be in the range 590-2760 depending on reaction conditions. Even when the reaction conditions were choosen to avoid adventitious terminating agents from atmosphere as well those present as impurities in monomers, there was no significant improvement in the copolymer molecular weight. Reaction variables such as temperature , different solvents, slow addition of monomers, addition of a nucleophile to the reaction mixture did not improve the copolymer molecular weight. The MeOXO-AA monomer system did not behave as one with living characteristics.

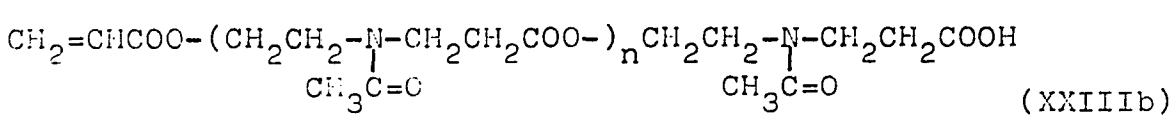
OXO-BPL system also polymerized to give only low molecular weight copolymers. Similarly, OXO-AA system polymerized to give gummy materials , but the product became insoluble after purification and drying.

Proton NMR , IR and ^{13}C NMR provided strong evidence for the MeOXO-AA copolymer to have the repeat unit structure , $-(CH_2CH_2-\underset{\underset{CH_3C=O}{|}}{N}-CH_2CH_2COO)_n$ with carboxylic (COOH) , acetamido ($-NHCOCH_3$) and olefinic ($CH_2=CHCOO$) end groups. Proton NMR also indicated , the copolymer to have a 1:1 alternating structure.

Analytical HPLC of the purified copolymer showed the presence of about 13 different fractions of which 10 were isolated by preparative HPLC. 300 MHz proton NMR analysis of these fractions indicated that the HPLC separation is based on a combination of factors including molecular weight and end groups. Fractions containing acetamido end groups elute from the column in increasing order of molecular weight. For lower DP fractions those with acetamido end groups elute after those with carboxyl end groups. when the DP is the same for the two types of fractions. However, the reverse is true for higher DP fractions. Based on the characterization and HPLC results, the following structures are proposed for the MeOXO-AA copolymer.



(XXIIIa)



(XXIIIb)

The above structures were further confirmed by isolating N-(2-hydroxyethyl)-β-alanine as the main hydrolysis product expected from the repeating unit structure. Presence of acrylic acid and acetic acid among hydrolysis products was proven by analytical HPLC and gas chromatography. Presence of ethanolamine in the hydrolysis products

was confirmed by isolating it as the dibenzoyl derivative. Based on these results it can be concluded that the MeOXO-AA copolymer consists of varying sizes of copolymer chains XXIIIa and XXIIIb.

Results of the direct NMR analysis experiment provided evidence tc consider the involvement of genetic zwitterion intermediate , as the species responsible for initiation and propagation. The observation of acetamido NH and methyl protons in the reaction mixture after only two hours at 60°C confirms the early termination reaction with XXXIII yielding polymer chains such as XXIIIa with olefinic and acetamido end groups.Reaction of a growing macrozwitterion with acrylic acid results in a terminated polymer chain such as XXIIIb with olefinic and carboxyl end groups.These termination reactions are responsible for limiting the copolymer molecular weight in the zwitterion polymerization of MeOXo-AA monomer system. The proposed polymerization mechanism is consistent with all of the experimental results.

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