PREPARATION OF CERTAIN HIGHLY STEREOSPECIFIC POLYMERS OF ACRYLIC, METHACRYLIC AND ITACONIC ACIDS AS POTENTIAL ANTITUMOR AGENTS

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1972

Submitted to the Faculty of the Graduate College
of the Oklahoma State University
in partial fulfillment of the requirements
for the Degree of
MASTER OF SCIENCE
July, 1976

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PREPARATION OF CERTAIN HIGHLY STEREOSPECIFIC POLYMERS OF ACRYLIC, METHACRYLIC AND ITACONIC ACIDS AS POTENTIAL ANTITUMOR AGENTS

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ACKNOWLEDGEMENTS

I wish to express my deep love and gratitude for my departed father whose encouragement and concern was wholly responsible for my success.

My sincere thanks is also due to Dr. E. M. Hodnett for his help and guidance in my research.

I would like to thank Majid, my husband, for his continued interest and support. The constant love and affection of my family which have been a sustaining force in the course of my degree studies are gratefully acknowledged.

I am highly thankful to Dr. O. C. Dermer for proofreading this thesis. I gratefully acknowledge Dr. K. D. Berlin and Dr. T. E. Moore for serving as members of my Advisory Committee.

Special thanks is expressed to the following for Summer Fellowship: Alumni Fellowship, Summer 1975 and Gulf Oil Co., Summer 1976. I am also thankful for the financial support from the Chemistry Department in the form of a Teaching Assistantship throughout my graduate career. I sincerely thank my fellow graduate students, particularly Prem Vuppalapaty, for their comments and suggestions during my study.

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CHAPTER I

INTRODUCTION

The great changes in the properties of polymers which result from ordered polymerization (94) led us to undertake the stereospecific polymerization of acrylic and methacrylic esters. Isotactic poly(acrylic acid) and poly(methacrylic acid) were prepared from isotactic poly(butyl acrylate) and poly(methyl methacrylate) respectively. Syndiotactic poly(acrylic acid) and poly(methacrylic acid) were also prepared by hydrolysis of the corresponding esters.

The potentiometric titration behavior of a polyelectrolyte solution is complex, needing for its explanation the consideration of first (61, 72, 77) and possibly second-neighbor interaction (73). A comparison of electrolytes differing only in stereospecificity is of considerable interest. The theory for this has been developed by Lifson (74).

Recently the difference between stereoregular and atactic poly(acrylic acid) has been studied (88). No difference in the potentiometric titration between solutions of the two forms was found. The marked difference in titration behavior between isotactic and "atactic" poly(methacrylic acid) as compared to the absence of such a difference in the case of poly(acrylic acid) may tentatively be attributed to the special steric effects in the case of poly(methacrylic acid) (124). The outstanding differences between isotactic and atactic poly(acrylic acid) are (a) ability of isotactic acid to crystallize and, (b) its lower solubility. Isotactic poly(acrylic acid) also differs from atactic polymer in the precipitation temperature and in the effect of neutralization and viscosity.

In 1968 De Somer _et al_. (25, 26) compared the antiviral activities of poly(acrylic acid) and poly(methacrylic acid) with those of other types of synthetic polyelectrolytes (e.g., dextran). They found that poly(acrylic acid) and poly(methacrylic acid) are more antivirally active than the other poly anions.

The aim of our study was to synthesize some stereospecific polymers in order to examine the change of their molecular structure with polymerization conditions (initiator, solvent, and temperature) and also to investigate differences in the biological activities, if any, between atactic and stereoregular structures.

CHAPTER II

HISTORICAL

In 1958 Fox and co-workers (27) reported the synthesis of crystallizable poly(methyl methacrylate) by free-radical as well as anionic polymerization. Depending upon the reaction conditions, they obtained three different polymers to which the following configurations could be assigned according to x-ray analysis (114).

Type I: Syndiotactic, obtained with 9-fluorenyllithium at -60° in 1,2-dimethoxyethane, and also in free-radical polymerization at low temperature.

Type II: Isotactic, obtained with 9-fluorenyllithium at -60° in hydrocarbon solvents, for instance, toluene.

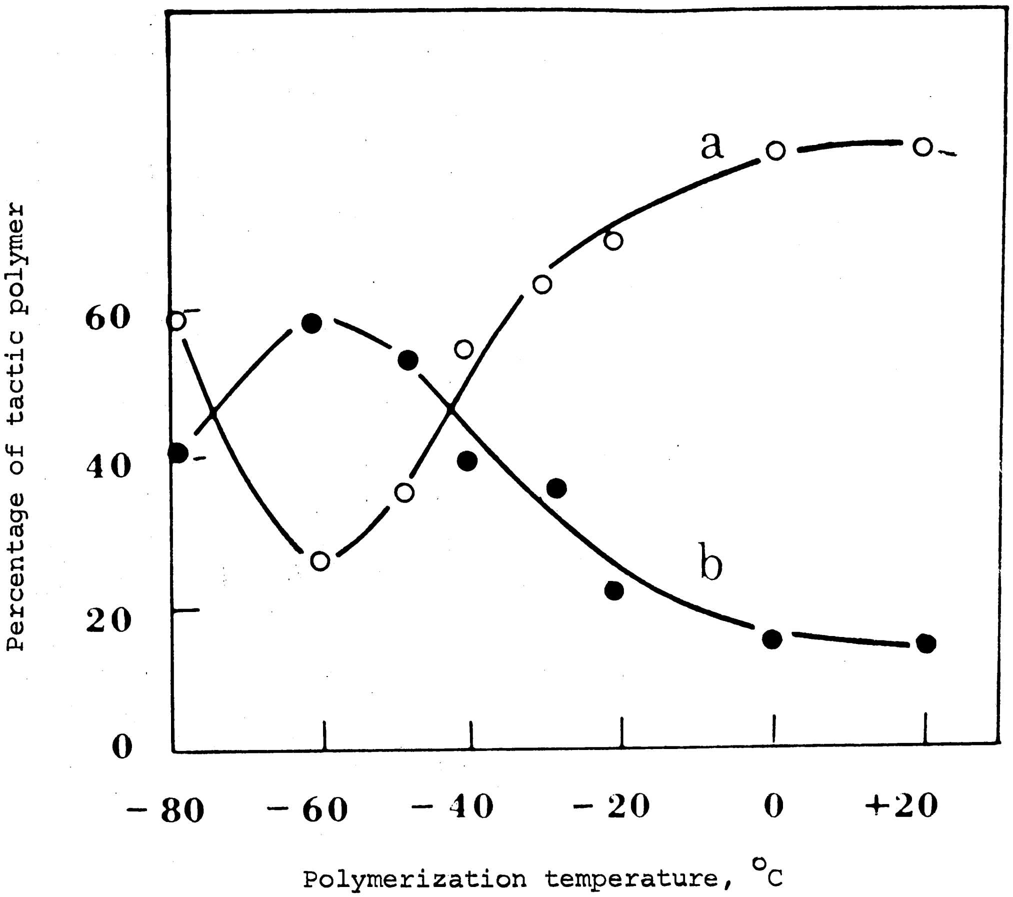
Type III: A block copolymer consisting of isotactic and syndiotactic blocks formed with 9-fluorenyllithium at low temperature (-70°) in toluene in the presence of small amount of dioxane.

Numerous later investigations with different initiator systems all showed that anionic polymerization of methyl methacrylate in nonpolar solvents yields primarily isotactic polymer, whereas in polar solvents syndiotactic propagation is favored. Besides metallic sodium and alkali metal-alcohol, organometallic compounds of the alkali metals were the initiators primarily employed in stereospecific polymerization of methyl methacrylate. In polymerizing methyl methacrylate at the surface of solid sodium in toluene at 30° Okamura and Higashumura (96) found an acetone-insoluble portion of polymer that exhibited x-ray crystallinity. This comprised up to 12.8% of the entire polymer formed, the amount depending upon the monomer concentration. According to Gall and McCrum (38), syndiotactic polymer is formed under these conditions.

The kinetics of the methyl methacrylate polymerization with organo-alkali metal compounds are difficult to follow because of rapidity of these reactions and because of possible side reaction of the initiator with the ester group of the monomer. Trekonal and Lim (117) overcame these difficulties by using as the initiator the lithium salt 1,1-dimethylbutanol. With this initiator they obtained highly isotactic polymers in toluene at temperatures between -60° and -20°. The <u>tert</u>-butyl methacrylate polymer was found to be less stereoregular (9).

The first to investigate intensively the stereospecific polymerization of methyl methacrylate initiated by organometallic compounds were Goode and co-workers (45). They observed that as the solvent was changed from tetrahydrofuran to 1,2-dimethoxyethane to diethyl ether to toluene, the type of poly(methyl methacrylate) obtained changed from syndiotactic to isotactic polymer. Korotkov and co-workers (65) observed similar results using other solvents. Thus, in the case of weakly solvating solvents such as toluene and hexane isotactic poly(methyl methacrylate) is obtained with <u>n</u>-butyllithium. When strongly solvating solvents such as liquid ammonia and pyridine are used, syndiotactic polymer results. With solvents of medium solvating power such as diethyl ether and ethylene glycol dimethyl ether, block polymers of these two configurations are obtained in various proportions. In toluene isotactic polymer is predominantly formed whereas in mixtures of toluene and tetrahydrofuran the fraction of isotactic links decreases rapidly with increasing proportion of tetrahydrofuran (43, 44). Highly stereospecific catalysts are relatively insensitive to changes in temperature, but the stereoregulating ability of less stereospecific catalysts is changed by changing the temperature. When isobutylmagnesium bromide initiates the polymerization of methyl methacrylate, the tacticity of the polymer is the same whether the temperature is -78° or 0° but when isobutylmagnesium chloride, a less sterospecific catalyst, is used the polymer obtained at 0° is more isotactic than the one at -78°. The manner in which polymerization temperature affects the tacticity of poly(methyl methacrylate) is shown in Figure 1, which is based on the data of Watanabe and associates (95).

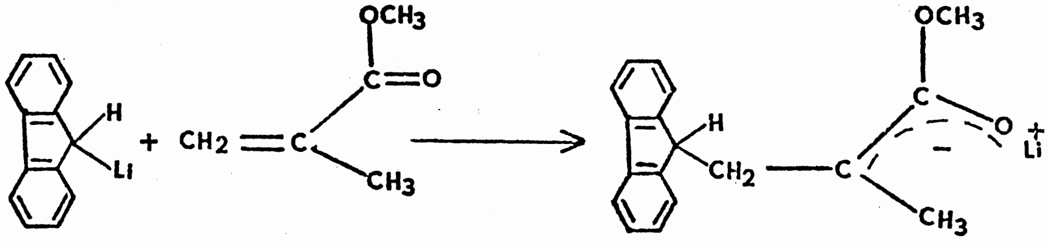
These workers used NMR spectroscopy to measure tacticity and expressed their results as percentages of the three triads, ddd or lll (isotactic), ldl or dld (syndiotactic) and ddl, dll, lld, or dld (heterotactic). It can be noticed that the percentage of isotactic polymer decreases as the polymerization temperature decreases from +20° to -50° (curve a). As seen by comparison to curve b which is a plot of the percentage of syndiotactic polymer against the temperature of polymerization, the decrease in isotacticity is accompanied by a parallel increase in syndiotacticity. The effects of temperature on stereoregularity have been discussed by Fordham (33) and Matsumoto (78). It was indicated that syndiotactic propagation should be slightly favored energetically over isotactic in free species (32). In the polymerization of methyl methacrylate with 9-fluorenyllithium in toluene Glusker and co-workers (40) obtained polymers that, according to spectroscopic analysis, had one terminal fluorenyl group per macromolecule. Initiation takes place via a form of Michael reaction by addition of the alkyl group of the



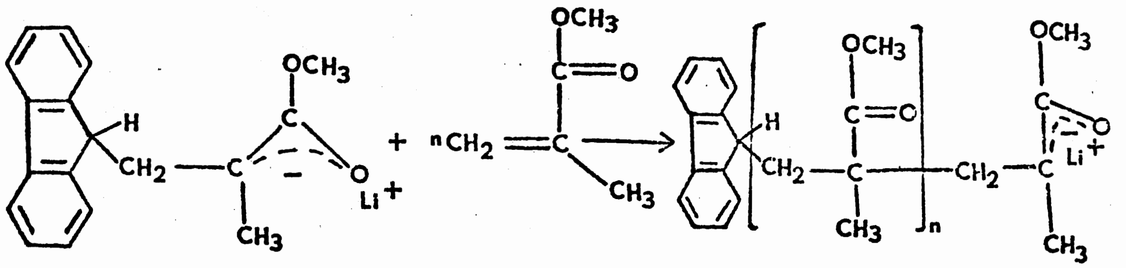
Curve a: Percentage of isotacticity.
Curve b: Percentage of syndiotacticity (data from Nishiaka, Watanabe (95)).

Figure 1. Tacticity of Poly(methyl methacrylate) Polymerized in the Presence of n-Pentyl Magnesium Bromide at Various Temperatures.

initiator to a monomer molecule.



Propagation now occurs by further addition of the monomer.



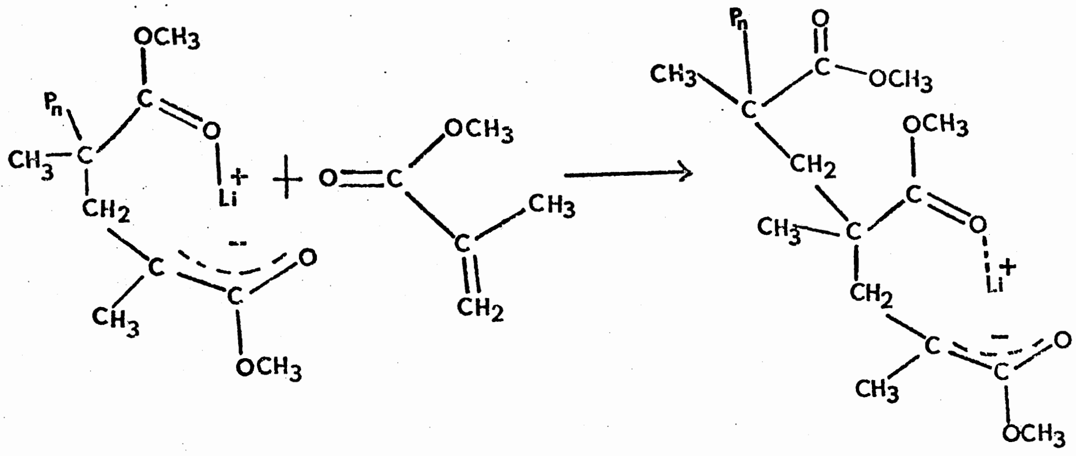
The termination reaction is extremely slow under the usual conditions of polymerization, and chain transfer with monomer is of little significance. The kinetics of methyl methacrylate polymerization with organolithium initiators have been investigated by several authors. According to Wiles and Bywater (126, 127), the reaction is complicated in that the initiator may cleave the ester group to yield methylate anion, which affects the tacticity of the polymer. The extent of additon of n-butyllithium to monomer carbonyl group is small under the polymerization conditions in n-hexane, but in tetrahydrofuran it is not to be neglected entirely (62). A more simple kinetic behavior is displayed when 1,1-diphenylhexyllithium is used as the initiator, since here an attack on the ester group is hindered (107). Braun and co-workers (18) compared the initiator effects of several alkali-metal alkyls. With alkyl lithiums in toluene they obtained polymers with a high fraction of isotactic linkage of monomer units. In initiation with alkyl sodiums or potassiums, on the other hand, the frequency of isotactic links decreased and that of syndiotactic links increased. The fraction of monomer units with heterotactic links increases with the alkali metal employed in the order lithium, sodium and potassium, which means that the stereo-specificity of the alkali metal alkyls decreases in the same order. In dimethoxyethane and in pyridine mainly syndiotactic polymers are formed, with the proportion of heterotactic links also increasing from lithium to alkali metal of higher atomic weight. Poly(methyl methacrylate) obtained with potassium alkyls are nearly atactic. From these findings it is evident that the stereospecificity of the propagation reaction does not depend solely on the extent of polarization of the carbon-metal bond and on the solvation of the terminal anionic groups of the chain, but is influenced also by the radius of the cation.

Despite numerous studies, the mechanism of the stereospecific polymerization of methyl methacrylate with alkali metal alkyls is not yet completely clarified. In fact, we have no more than hypothetical concepts regarding the causes of stereoregulation (118). According to Glusker (41) isotactic linking of monomer molecules in polymerization initiated by alkyl lithiums is due to the formation of a complex of the lithium counterion with the carbonyl oxygen of both ultimate and penultimate ester group. In the presence of Lewis bases, the formation of this complex is inhibited and a decrease in isotacticity results. Cram and Kopecky (23) assume an enolization of the active chain end resulting in a cyclic structure.

It is necessary to consider the type of ionization that occurs in the metal-carbon bond in these initiators. Thus, neglecting intermolecular association, we may represent the ionization of alkyllithium derivatives as follows (129):

RLi	R^-Li^+	R^-/Li^+	$R^- + Li^+$
covalent	intimate-ion pair	solvent-separated ion-pair	free ions
I	II	III	IV

In solutions of low dielectric constant, it would be expected that forms I and II would be predominant. These forms should initiate polymerization at a slower rate and with more steric requirements than forms III and IV. The later should predominate in polar solvents. When reaction conditions favor stero-regularity, the covalent and the intimate ion-pair forms generally lead to the isotactic structure (nonpolar solvent). As the polarity of the medium increases, the syndiotactic placement is favored at low temperatures. Temperature also affects the equilibrium between forms II and III. In more polar solvents, the polymeric anion may be considered to be a free propagating species and the requirements for stereospecific polymerization should be similar to those formulated for free-radical interaction. In free-radical polymerization, Bovey (11) found that for methyl methacrylate syndiotactic propagation became increasingly important as the reaction temperature was lowered. The activation energy for the isotactic placement was about 0.8 kcal/mole greater than for syndiotactic placement. Once the alkyllithium has reacted with a monomer e.g., methyl methacrylate, the growing polymeric alkyllithium may be expected to possess enolic character, as shown in the following equation:



Also, the lithium atom can coordinate with the carbonyl oxygen of the penultimate monomer unit. The cyclic intermediate involves intramolecular solvation of the lithium atom, and because of intramolecular shielding of one side of the lithium atom, nucleophilic attack by monomer unit will take place on the opposite side to give a transition state which is analogous to that of S_N2 reactions. As the bond-forming reaction between lithium and the incoming olefin develops, the O-Li coordinate linkage will break. Simultaneously, the polymer anion will migrate from the lithium atom to the methylene group of the monomer molecule. The newly formed lithium enolate system is then rapidly stabilized by intramolecular solvation. In this way, configuration retention will be maintained providing that the monomer molecule always presents the same conformation toward the lithium atom. For methyl methacrylate, it appears that the conformation involving the least steric hindrance is the one in which the α-methyl group is trans to the α-methyl group of the carbanion as depicted in Figure 2.

In the absence of an α-methyl group, the latter condition would not be attained and it would be difficult to form an isotactic polymer,

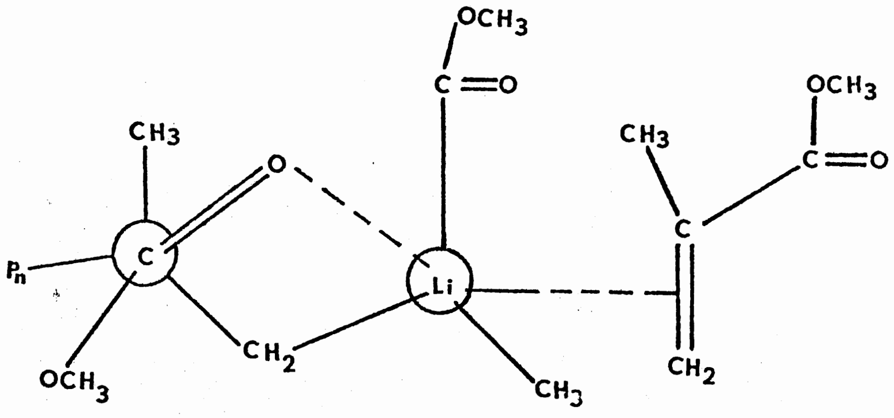
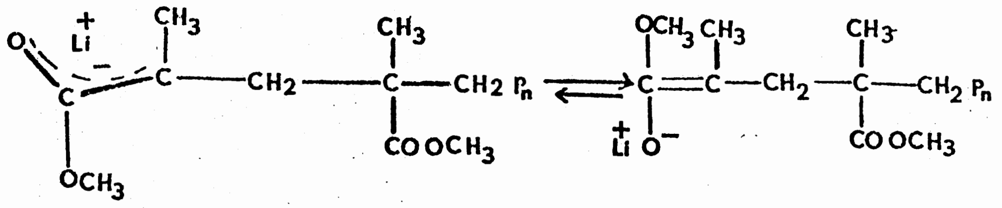


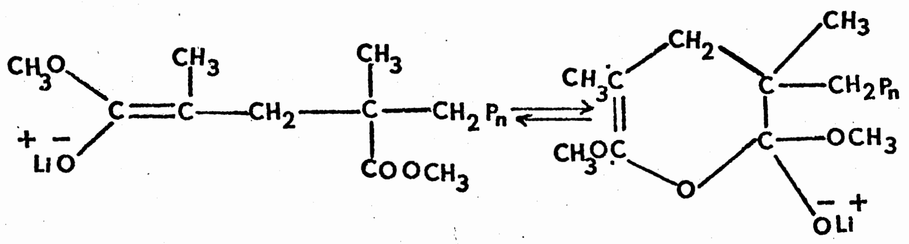
Figure 2. Preferred Monomer Conformation in an S_N2-Type Reaction With a Lithium Atom(5)

e,g., in the case of methyl acrylate. For other acrylate monomers in which branching at the α-carbon of the ester group occurs, e.g., isopropyl acrylate, similar requirements for stereospecific polymerization will apply. In such cases, monomer conformation will be determined by the bulky ester group, which shields one side of the double bond and causes the opposite side to approach the lithium atom. Cram and Kopecky (23, 24) proposed a mechanism in which the growing lithium enolate is considered to have a great amount of alkoxide character and this is stabilized by the formation of a six-membered ring due to attack of the alkoxide group on the carbonyl group of the penultimate monomer units (Equations 1 and 2). Stereospecific growth is then believed to proceed by means of Diels-Alder type reactions in which the six-membered ring is destroyed while a new ring is formed simultaneously, as in Equation 3.

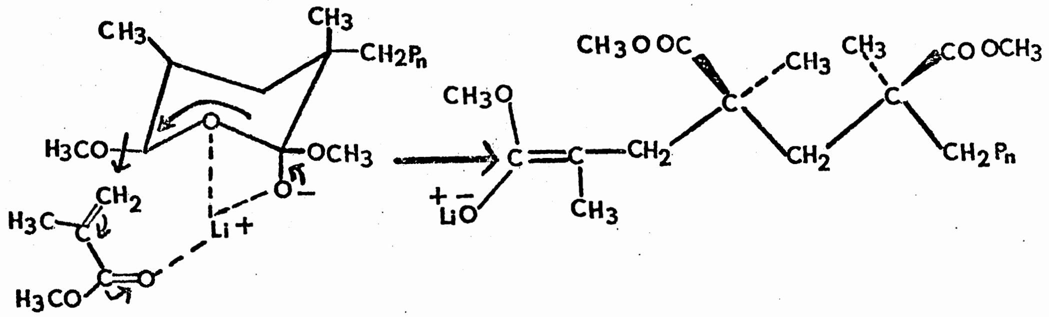


(1)

P_n = Chain with 'n' units)



(2)



(3)

Scott (111) found that sodium and other alkali metals form intensely colored 1:1 complexes with aromatic hydrocarbons such as naphthalene, biphenyl, and anthracene. Recently (128), the polymerization of methyl methacrylate in toluene by means of 1,1-diphenyl-n-hexyllithium was studied. Rapid formation of low-molecular-weight polymer was found. It seems plausible to assume that the attack of 1,1-diphenyl-n-hexyllithium on monomer carbonyl groups would be small owing to steric factors and that there could therefore be a large difference between the polymerizations of methyl methacrylate initiated by n-butyllithium and by 1,1-diphenyl-n-hexyllithium. Such differences have been found: the formation of alkoxides was much less in the case of 1,1-diphenyl-n-hexyllithium and no bimodel molecular weight distribution was observed for polymer produced by 1,1-diphenyl-n-hexyllithium. The stereospecificities of the polymers produced by the two catalysts were different in degree. The kinetic relationships obtained were not as complex for 1,1-diphenyl-n-hexyllithium as for n-butyllithium. Thus, for the former, the polymerization rate was first order in both monomer and initiator concentration up to at least 70% monomer consumption. Kinetic data obtained from experiments at 0^{o}, -30^{o} and -80^{o} are summarized in Table I.

Since there is much less formation of alkoxide with 1,1-diphenyl-n-hexyllithium, attack on the vinyl double bond occurs to a larger extent. Furthermore, it is assumed that the interaction is rapid and that there exists a steady concentration of growing polymer chains which is a constant fraction of the 1,1-diphenyl-n-hexyllithium added, the first-order dependencies would be expected. Evidence for this has been obtained by Glusker and co-workers (40, 41) and is shown in Table II. This table is a summary of results which indicate how the isotacticity of poly(methyl methacrylate) varies according to the initial monomer initiator concentration ratio and, hence, according to the concentration of lithium methoxide.

The discovery in 1958 of a crystalline form of poly(methyl methacrylate) prepared with the free-radical initiator at a low temperature focused attention on this topic and indicated that free-radical polymers did not necessarily have the random atactic structure that was usually assumed. The factors which control the orientation of the incoming monomer molecules in free-radical polymerization namely, steric or dipole interaction, are not as important as in ionic polymerization. In most

TABLE I

POLYMERIZATION OF METHYL METHACRYLATE BY 1,1-DIPHENYL-*n*-HEXYLLITHIUM IN TOLUENE

Run	1,1-Diphenyl-*n*-hexyllithium mole liter^{-1} x 10^3	Methyl methacrylate mole liter^{-1}	Polymerization Temperature $^{\circ}$C	-d ln [Methyl methacrylate]/dt min^{-1} x 10^2
1	3.2	0.125	-30	11.10
2	1.6	0.125	-30	5.60
3	1.6	0.125	-30	5.50
4	0.8	0.125	-30	2.80
5	2.4	0.125	-80	0.29
6	2.4	0.125	0	13.00

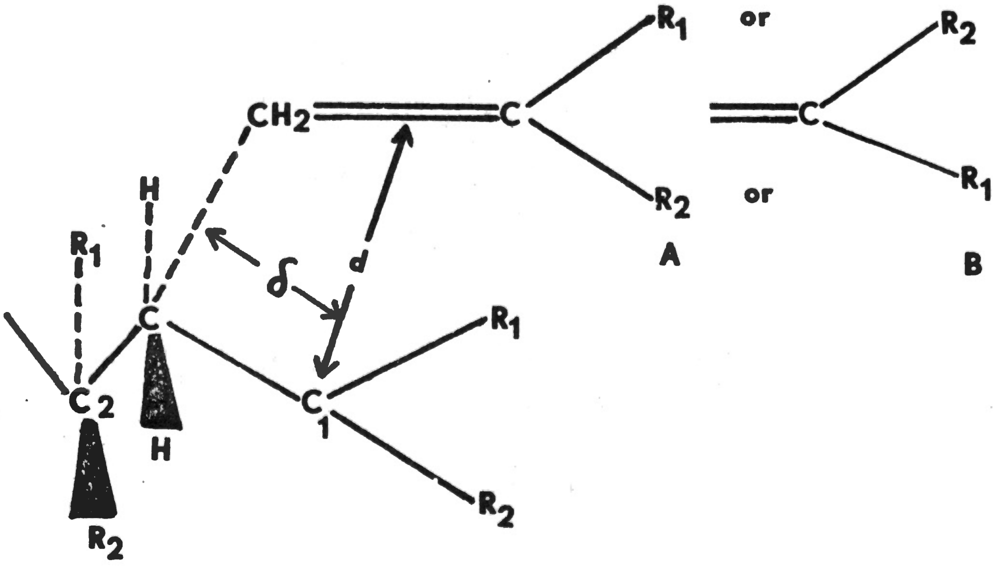
TABLE II

EFFECT OF POLYMERIZATION CONDITIONS ON POLYMER TACTICITY(128)

1,1-Diphenyl-*n*-hexyllithium mole liter^{-1} x 10^{3}	Methyl methacrylate mole liter^{-1}	Polymerization Temperature ^{o}C	Conversion %	% Triads		CH_3OH mole liter^{-1} x 10^{3}
				I	S	
3.2	0.125	-30	100	88	4	0.6
1.6	0.125	-30	100	85	3	0.3
1.6	0.250	-30	91	84	3	0.3
0.8	0.125	-30	72	87	3	0.1
2.4	0.125	-80	70	87	3	0.4
2.4	0.125	0	32	76	5	0.5
n-Butyllithium mole liter^{-1} x 10^{3}						
7.6	0.250	-30	100	71	12	6.7
7.6	0.125	-30	100	82	8	5.3
3.8	0.250	-30	100	75	10	3.5

free-radical polymerization there is no intermediate complex of well-defined geometry in the addition of a monomer to the growing chain, such as exists in many ionic systems. The configuration of an entering monomer unit will be determined by its direction of approach, and preferred orientation may result if there are steric or electronic interactions between the substituents.

In fact, only if these are negligible in the transition state will a completely random structure be obtained. The addition to a polymer chain of successive units of D and L configuration can thus be linked to a copolymerization (100), and if there are significant energy differences between them, the composition, in terms of configurational isomers, will change with temperature. The addition of a monomer to a free-radical chain is shown diagrammatically as follows:



Presentation of the monomer with its substituents on the same side as those of the terminal carbon atom C-1 (mirror approach A) will give isotactic placement, whereas if these are on opposite sides (non-mirror approach B) syndiotactic addition will result (2). The geometry of approach of the monomer is further defined by the angle of its axis to that of the chain axis, the lateral distance, δ, between C-1 and the bonding carbon atom of the monomer, and the separation distance, d, between them. The configuration of C-1 is determined only at the moment of attachment of the monomer, and whether it is isotactic or syndiotactic depends on the configuration of the penultimate unit (carbon atom C-2). The minimum interaction between the substituents on C-1 and C-2 could favor one mode of addition over the other. This aspect of minimum steric interaction in the growing polymer chain in the propagation reaction has been emphasized by Cram and Kopecky (23). A more sophisticated attempt was made by Bawn <u>et</u> <u>al</u>. (7), who took into account the effect of sp^3 hybridization on the terminal carbon atom and the effect of radical addition at the end of the double bond (p-σ reaction, δ=0) as well as p-π/addition. Syndiotactic addition was found to be favored at all separation distances and was roughly in accord with experimental values (about 1 kcal) at 3 Å separation. Bawn, James and North (7) also calculated penultimate unit interactions.

Methyl methacrylate forms a polymer with considerable steric hindrance, and it was calculated that the energy barrier for rotation of the terminal unit exceeds 20 kcal/mole. This is much greater than the activation energy for propagation, so that the chance of a rotation occuring before addition of the next monomer molecule would be negligible. Two stable rotational isomers were predicted, one corresponding to syndiotactic addition and the other leading to isotactic arrangement, but in the latter case minimum energy necessitated a rotation of about 30° by the penultimate unit (C-2). The calculation indicated that with the planar sp^2 structure in the radical chain end, control of configuration would depend on the terminal unit-monomer interaction, but that if there were a substantial proportion of sp^3 character in the transition state the interaction energies between terminal and penultimate monomer unit would be increased. Even so, syndiotactic addition would be favored by about 1.5 kcal/mole.

Fox and co-workers (27) found that poly(methyl methacrylate) formed by light or a free-radical-initiated reaction showed a progressive change in infrared spectra with polymerization temperature, and samples prepared below 0° were crystalline. The infrared assignments were not absolute measurements, and x-ray data could give no more than an indication of the degree of tacticity, but Fox et al. suggested that syndiotactic addition was favored by 1-2 kcal/mole (28). The first determination of the configuration of the polymer was made by Bovey (11) using high-resolution NMR. From the temperature dependence of the structure it was estimated that $DH_s^i = 0.75$ kcal/mole and $DS_s^i = 0$. Fox and Schnecko (29) subsequently reported slightly different values, $DH_s^i = 1.07 \pm 0.05$ kcal/mole and $DS_s^i = 0.99 \pm 0.1$ eu, but the estimates of isotactic addition do not differ greatly, as can be seen from the data in Table III.

Watanable found DH_s^i from the infrared spectra to be comparable but somewhat higher at 1.38 - 1.44 kcal/mole (122). The predominance of syndiotactic structure in poly(methyl methacrylate) is thus firmly established, although even at the lowest temperature employed average sequence lengths of less than ten are to be expected. The relative proportion of isotactic, syndiotactic, and heterotactic triads in these polymers indicated that the stereochemistry of the addition step was controlled only by the interaction of the terminal radical with the incoming mono-

TABLE III

TEMPERATURE DEPENDENCE OF ISOTACTICITY IN POLY(METHYL METHACRYLATE) MADE WITH FREE-RADICAL INITIATION

Polymerization Temperature °C	Isotacticity, I	
	Bovey(11)	Fox and Schnecko(29)
-78	0.13	-
-40	-	0.14
0	0.22	-
50	0.24	-
60	-	0.24
100	0.27	0.27
150	-	0.33
250	-	0.36

mer.

If the proportion of the triads DDD and LLL; DLD and LDL; and DDL, DLL, LLD, and LDD are represented by P_i, P_s, and P_h, it is clear that the probability of an isotactic triad, P_i, will be related to the isotacticity, I, which refers to diads, by $P_i = I^2$, and that $P_h = 2\ I(1-I)$. The relationship is used to test whether the polymer stereochemistry has a statistical distribution determined only by the terminal chain unit (21).

The structure of poly(methyl methacrylate) appears to be independent of whether it is polymerized in bulk or in solvents such as toluene, acetaldehyde, and ether (6); this suggests that solvents do not participate in the propagation reaction, although there is some evidence to indicate that they complex with the monomer (110).

The interactions that lead to mainly syndiotactic polymer change markedly where polymerization is carried out at very low pressures, or at very low temperatures when the monomer is frozen. Thus, isotactic poly(methyl methacrylate) has a higher density than the syndiotactic form (1.23 g/ml compared with 1.18 g/ml) and would be the favored structure in polymerization at very high pressures. Zulov et al. (134) have found that polymers produced at high pressures indeed have a higher density than normal and the isotactic fraction changes from 0.25 at atmospheric pressure (polymerization temperature 51°) to 0.48 at 8000 kg/cm^2 pressure (121). At temperatures in the region of -100° in the presence of magnesium metal (58) or zinc chloride with photoinitiation (59) a crystallizable polymer was obtained, claimed to be isotactic from its density, glass-transition temperature, and x-ray diffraction pattern. The reaction was inhibited by hydroquinone, and a free-radical mechanism is probable. It was suggested that zinc chloride aids the formation of a helix by coordination with a pair of methoxyl groups in the propagating chain as shown as in Figure 3.

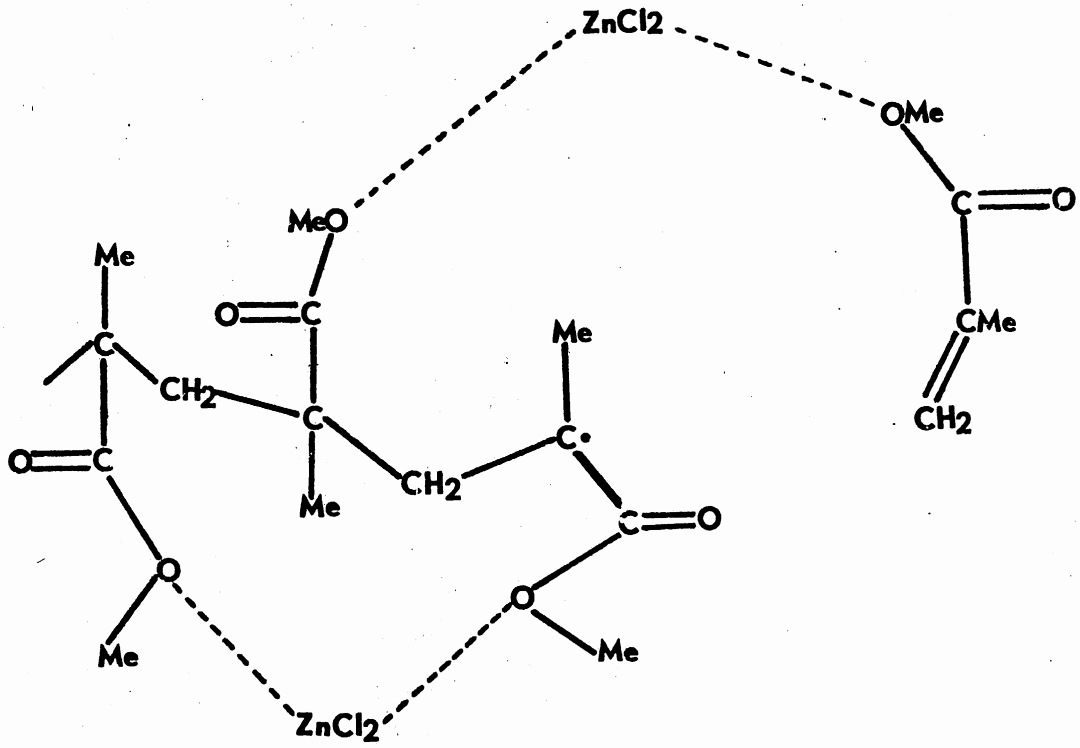


Figure 3. Formation of a Helix by Coordination With a Pair of Methoxyl Groupings in the Propagating Chain.

Later work, however, has thrown considerable doubt on these findings. A polymer prepared under similar conditions by Bovey (12) was predominantly syndiotactic, and Bovey suggested that Kargin et al. assigned the wrong structure to the polymer.

Imoto et al. (52) reported that a complex is formed between monomer and zinc chloride but stated that its effect is only to increase the rate of polymerization (K_p is increased by a factor of about three) (10). The crystallinity of the polymer was not affected by the presence of zinc chloride. Polymer tacticities were found to be independent of zinc chloride concentration whether polymerization was conducted in bulk, in ethyl acetate solution, or in aqueous suspension (116). Values obtained (using NMR) were very comparable with those obtained in the absence of zinc chloride, and, since the relationship $P_h = 2 I (1-I)$ was found to hold, the configuration of the growing chain is determined only by the last unit in the propagating chain. The 1:1 complex of methyl methacrylate and zinc chloride gave a less syndiotactic polymer, but it was more nearly atactic in structure than stereospecific.

Benzophenone ketyls, too, initiate the polymerization of methyl methacrylate (53, 133). If tetrahydrofuran or dimethoxyethane is used as the solvent, polymers in which syndiotactic links somewhat predominant over isotactic ones are obtained. According to Tsuruta and coworkers (118), highly isotactic polymer is formed with the sodium ketyl (not, however with the lithium or potassium ketyl) at -70°. In tetrahydrofuran or dimethoxyethane, polymerization of methyl methacrylate is also initiated by radical ions obtained from arenes and alkali metals. With increasing polymerization temperature the amount of syndiotactic linkage decreases. Furthermore, the lengths of the syndiotactic sequence decrease with the type of alkali metal in the order: Li > Na > K > Cs (48).

Methyl acrylate and acrylic acid as well as methacrylic esters having bulky alkyl ester groups are also subjected to stereospecific polymerization. Thus crystalline poly(isopropyl acrylate) and poly-

(isopropyl methacrylate) can be prepared by polymerization with organolithium or organomagnesium compounds. According to Miller and Rauhut (88) tert-butyl acrylate yields a crystalline product with lithium dispersion or n-butyllithium, whereas methyl acrylate as well as normal, secondary, and isobutyl acrylate yield amorphous polymers. Polymerization of normal and tert-butyl methacrylates by n-butyllithium at -50° yields isotactic polymer, and sodium naphthalene in tetrahydrofuran and lithium in liquid ammonia lead to syndiotactic polymer (3). Polymerization of phenyl methacrylate by butyllithium in toluene at -30° gives an isotactic polymer (71).

Nishioka et al. (95) observed that the stereoregularity of poly (mehtyl methacrylate) can be controlled over a wide range by selecting Grignard reagents with appropriate alkyl groups and suitable reaction temperatures. Thus, isotactic polymer was obtained when Grignard reagents were used that contained branched alkyl groups such as isobutyl, secondary, butyl and cyclohexyl at -80° to +20° or with phenylmagnesium bromide at ambient temperatures. Stereoblock polymer containing isotactic and syndiotactic units could be synthesized by the use of a reagent with a linear alkyl group, e.g., n-butyl magnesium bromide.

Above room temperature, the rate of polymerization is high and large amounts of catalyst are required. The alkyl groups on the Grignard reagent are listed in the order of decreasing polymerization rate they cause.

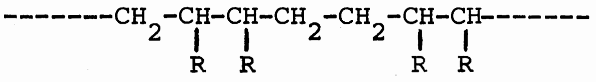
In ether solution:

sec.-octyl > sec.-butyl > isopropyl > isobutyl > n-octyl > phenyl > ethyl > n-butyl > n-propyl > tert-butyl.

In toluene solution:

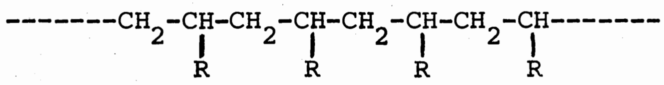
sec.-octyl > sec.-butyl > isopropyl > isobutyl > phenyl > tert.-butyl > n-octyl > ethyl > n-butyl > n-propyl.
The polymerization rate increases over the range -50° to -25° but decreases above -25°.

Monomers of the formula $CH_2 = CHR$ may polymerize in either of two ways to give Structure 1 or 2 or mixture of these forms.



$$\text{-------}CH_2-\underset{R}{\underset{|}{CH}}-\underset{R}{\underset{|}{CH}}-CH_2-CH_2-\underset{R}{\underset{|}{CH}}-\underset{R}{\underset{|}{CH}}\text{-------}$$

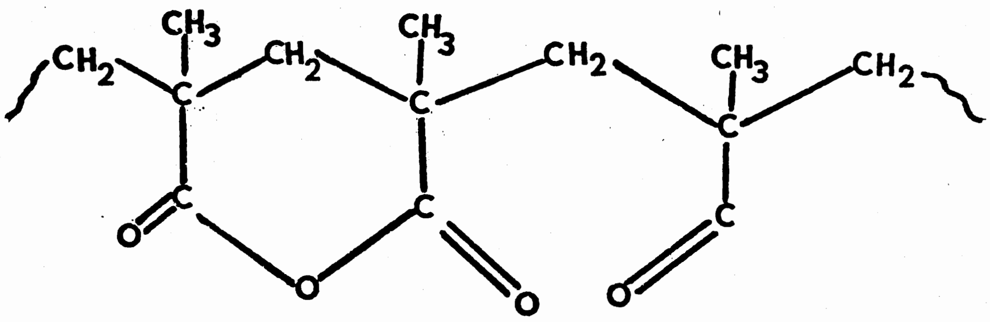
Structure 1



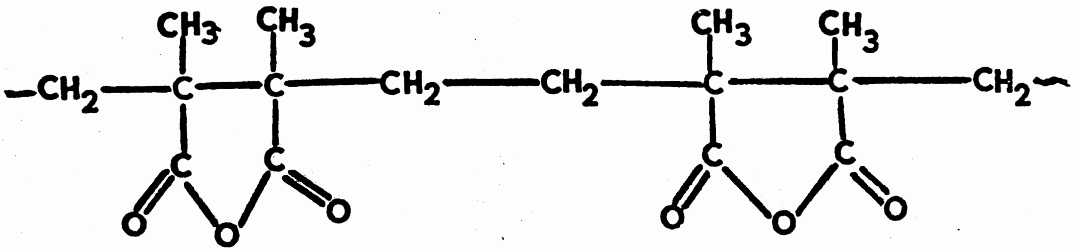
$$\text{-------}CH_2-\underset{R}{\underset{|}{CH}}-CH_2-\underset{R}{\underset{|}{CH}}-CH_2-\underset{R}{\underset{|}{CH}}-CH_2-\underset{R}{\underset{|}{CH}}\text{-------}$$

Structure 2

Structure 1 is head-to-head (tail-to-tail) and Structure 2 is head-to-tail. Experiment shows that vinyl polymerization in the presence of ionic or free-radical initiators occurs almost exclusively head-to-tail. Anhydropoly(methacrylic acid) prepared by dehydration of poly(methacrylic acid), was examined by IR spectroscopy (47). The examination showed that only the six-membered rings of Structure 3 were present, and not the five-membered rings of Structure 4. Since head-to-tail linkage would have formed six-membered rings, the Structure 3 was supported.



Structure 3



Structure 4

Stereoregularity has such a marked influence on the melting points of polymers that a method of estimating isotacticity from melting points has been suggested (19). In general the packing density is greater for syndiotactic polymer than the corresponding isotactic conformation and this results in a higher melting point (49). Melting points as a function of tacticity for several polymers are listed in Table IV. It follows that atactic polymers exhibit lower melting points than those of their isotactic species.

When poly(methyl methacrylate) films were degraded in a temperature range of 275° - 400°, it was found (56) that the chain length of the isotactic species was about 20 times that of the syndiotactic species. The physical properties of these polymers depend to a large degree on the type of alcohol from which the acrylic or methacrylic ester has been prepared. Poly(methyl acrylate) is a tough, rubbery and fairly hard polymer forming a plastic film that can be stretched 750%. *n*-Butyl acrylate polymers are the first in the acrylate series to display tackiness. In contrast to the softness of poly(methyl acrylate) the polymer of methyl methacrylate is a hard material. Its glass transition temperature, T_g, melting point, T_m, and density, d, are listed in Table V. The second order transition temperatures for the polymer of methyl methacrylate and methyl acrylate are listed in Table VI.

Some polyanions possess antitumor (93, 102, 103, 104) and antiviral

TABLE IV

MELTING POINTS VS. TACTICITY OF POLYMERS (107)

Polymer	Melting point, °C	
	Syndiotactic	Isotactic
Poly(tert.-butyl methacrylate)	150-160	100
cis-1,4-Poly(1,3-pentadiene)	52-53	44
1,2-Poly(1,3-butadiene)	154	120-125
Poly(methyl methacrylate)	$\geq$200	160

TABLE V

SOME PROPERTIES OF STEREOREGULAR POLY(METHYL METHACRYLATE)

	Glass Transition Temperature °C	Melting Point °C	Density g/ml
Syndiotactic	115	200	1.190
Isotactic	45	160	1.220
Stereoblock	60-95	170-190	1.20-1.22
Atactic	104	-	1.188

TABLE VI

SECOND-ORDER TRANSITION TEMPERATURE FOR POLYACRYLATES AND POLYMETHACRYLATES

Polyacrylate	Glass Transition Temperature °C	Polymethacrylate	Glass Transition Temperature °C
Methyl	3	Methyl	105
Ethyl	-23	Ethyl	47
_n_-Propyl	-51.5	_n_-Propyl	33
_n_-Butyl	-70	_n_-Butyl	17
_n_-Tetradecyl	20	_n_-Octyl	-70
_n_-Hexadecyl	35	_n_-Decyl	-70
		_n_-Tetradecyl	-9

activity (67, 68). Kleinschmidt *et al.* (105, 125) have shown induction of interferon by statolen, an anionic polysaccharide that inhibits Friend leukemia virus (125).

A divinyl ether-maleic anhydride copolymer of molecular weight 17,000, poly(pyran-3,4-dicarboxylic anhydride), is undergoing clinical trial against advanced cancer in man. Its animal and clinical pharmacology indicates uptake in the nucleated elements of the blood and stimulation of reticuloendothelial activity in liver, spleen, and bone marrow. The action of these polyanions may be similar to that of kidney bean phytohemagglutinin which similarly inhibits Friend virus splenomegaly (120), and which has been shown by Wheelock to induce interferon-like activity *in vitro* (50).

The action of polyanions may also be mediated through inhibition of enzymes important for viral adsorption. However, attempts to correlate anti-viral action with inhibition of ribonuclease, hyaluronidase, and anti-thrombin activity have not been successful (68, 105).

Anionic polysulfonates and polyphosphates of either natural or synthetic origin have been shown to be potent inhibitors of transplanted tumors in mice (4, 93, 101, 102). This inhibition of tumor growth may be a function of the density and distribution of ionic charges within the polyelectrolyte molecule. Two kinds of synthetic polymers were chosen: polycarboxylates derived from ethylene/maleic anhydride copolymers and those derived from polyacrylic acid. In most experiments, sarcoma 180 was the tumor system used. It appears that at least one ionizable carbonyl group is required for the polymer to manifest significant tumor inhibition. Tumor inhibition for the two polymer series was strongly dependent on carboxyl substitution which varied molecular configuration in solution. Within each series, charge density may govern tumor-inhibiting effectiveness and toxicity. Optimum activity was obtained where carboxamide and ionizable carboxyl groups were interdispersed along the polymer backbone. When all carboxyl groups are converted to carboxamides, significant loss in tumor inhibition was experienced. In addition, proper carboxamide-carboxyl balance broadens the scope of activity against a variety of transplanted tumors. Synthetic polyelectrolytes also inhibit certain vital enzymes such as ribonuclease and deoxyribonuclease (50, 51, 101). Clinically, the pyran copolymer has been given to more than sixty patients at a high dosage, 12 mg/kg/day. Pyran induces fever and blocks the conversion of fibrinogen to fibrin, but interestingly, no patient has suffered hemorrhage despite significant prolongation of clotting time. Pyran has interferon-inducing capacity and pretreatment prior to inoculation with Friend virus leukemia or Raucher leukemia inhibits subsequent tumor growth induced by these viruses. Similar inhibition of tumors has been found for acrylic acid and styrene-maleic anhydride copolymers (105).

CHAPTER III

EXPERIMENTAL

Materials

Benzene (Eastman). Reagent-grade benzene was dried over calcium hydride, distilled, and used as a solvent.

Butyl acrylate (Eastman). Lot # D4B was dried with anhydrous calcium sulfate and then distilled under reduced pressure.

Dimethyl itaconate (Aldrich Chemical Company). Lot # 10,953-3, assaying 97%, was dried over anhydrous calcium sulfate and then distilled under reduced pressure.

Fluorene (Eastman Kodak Co.). Technical-grade fluorene was crystallized from ethanol before use.

Methyl methacrylate (Amend Drug and Chemical Co.). Methyl methacrylate was dried over anhydrous calcium sulfate and then distilled under reduced pressure.

Tetrahydrofuran (Fisher Scientific Co.). Reagent-grade tetrahydrofuran was used as a solvent, purification was performed by refluxing over calcium hydride and then distilling.

Toluene (J. T. Baker Chemical Co.). Reagent-grade toluene was purified by refluxing over calcium hydride and then distilled.

n-Butyllithium (Foote, Mineral Co.): Lot # 708-18 1.6M in hexane.

The following reagents were used without further purification: acetone (Fisher Scientific Co.), 2,2'-azobis[2-methylpropionitrile]

(Matheson, Coleman and Bell), benzoin (Fisher Co.), calcium hydride (Matheson, Coleman and Bell), calcium sulfate anhydrous (W. A. Hammond Drierite Co.), chlorobenzene (Fisher Scientific Co.), ethanol (U.S. Industrial Chemical Co.), phenylmagnesium bromide (Arapahoe Co.), 3M in diethyl ether, 1-propanol (Fisher Scientific Co.), methylmagnesium bromide (Arapahoe Co.), 3M in diethyl ether, and sodium hydroxide (Mallinckrodt Chemical Works).

Instrumentation

Infrared spectra were obtained with a Beckman IR-5A spectrophotometer. Proton magnetic resonance spectra were obtained on a Varian model XL-100 analytical nuclear magnetic resonance spectrometer.

Potentiometric titrations were performed with a Beckman Research pH meter equipped with a Brinkman Instrument heater-circulator and thermoelectric cooler and a magnetic stirrer by Precision Scientific Co. Number-average molecular weight determinations were made using a Coleman 115 Molecular Weight Apparatus.

Preparation of Polymers

Preparation of 9-fluorenyllithium (115). 9-Fluorenyllithium was prepared by the exchange reaction between fluorene and *n*-butyllithium in dry toluene. The apparatus consists of a three-necked flask equipped with a magnetic stirrer, a condenser, a nitrogen inlet and a serum cap. Toluene (107.8 ml) dried over calcium hydride, was placed in the flask. Then 5.2 g (0.031 mole) of fluorene, previously purified by recrystallization, was added. To this mixture 1.76 g (0.0275 mole) of *n*-butyllithium in 17.2 ml of hexane was added by means of a hypodermic syringe. The reaction mixture was refluxed for 8 hours under nitrogen. The product was only slightly soluble in toluene and separated as a bright orange, finely divided solid. The solution was stored in a bottle sealed with a rubber serum cap.

Preparation of isotactic poly(methyl methacrylate) (I) (40,45). Methyl methacrylate (13 g, 0.13 mole) purified and dried over anhydrous calcium sulfate was placed in a three-necked round-bottomed flask equipped with a magnetic stirrer, a thermometer, and an inlet and an outlet for nitrogen gas. One neck of the flask was covered by a rubber serum cap. Then 170 ml of toluene, dried over calcium hydride and redistilled, was added. The flask was flushed with dry nitrogen and the contents were cooled to -60°. A 30-ml portion of a 0.22 M suspension of 9-fluorenyllithium (0.0066 mole) in toluene was added by means of a hypodermic syring inserted through the rubber cap. The temperature of the reaction mixture was maintained at -40° ± 6° for 6 hours. During this period the solution became viscous. A small amount (5 ml) of mehtanol was added in order to destroy the initiator, and the reaction mixture was permitted to warm up to room temperature. The polymer was precipitated by pouring the solution into 600 ml of methanol and water (6:1). The swollen solid which separated was redissolved in 100 ml of acetone, and precipitated in 500 ml of water. The solid was then dried under reduced pressure at room temperature. The polymer was then blended into a white powder. The yield was 8.6 g, 66% of theory.

Preparation of syndiotactic poly(mehtyl methacrylate) (II) (40,45). A three-necked round-bottomed-flask was equipped with a magnetic stirrer, a thermometer, and an inlet and an outlet for nitrogen gas. One neck of the flask was covered by a rubber serum cap. Tetrahydrofuran was separately refluxed for 24 hours over calcium hydride, then 250 ml of the dry solvent was distilled into the flask. Fluorene (0.83 g, 0.005 mole), previously purified by recrystallization, was added to the flask and a solution of n-butyllithium containing 0.0048 moles in 3 ml of hexane was transferred to the flask using a dry syringe. The mixture was stirred under nitrogen for 2.5 hours until the metalation of the fluorene was complete. The flask was then cooled to -70° (using dry ice and acetone) and 41.5 g (0.415 mole) of methyl methacrylate, dried and distilled under reduced pressure, was added. The polymerization was continued for 9 hours. The mixture became very viscous. Then 5 ml of methanol was added and the viscous solution warmed to room temperature. The solution was poured with stirring into 500 ml of petroleum ether and the solid was filtered off. The polymer was redissolved in benzene, reprecipitated with petroleum ether, and again filtered out. The solid was dried at room temperature and ground to a white powder. The yield was 33 g, 79% of theory.

Preparation of isotactic poly(butyl acrylate) (III) (86). Toluene (500 ml), dried over calcium hydride and redistilled, was placed in a four-necked round-bottomed flask equipped with a magnetic stirrer, a condenser, and an inlet and an outlet for nitrogen gas. One neck of the flask was covered by a rubber cap. Fluorene (0.80 g, 0.0048 mole), previously purified by recrystallization, was added, then the mixture was deoxygenated with nitrogen) for one hour. n-Butyllithium, 0.0048 mole in 3 ml of hexane, was added to the solution. The mixture was then refluxed for 45 minutes. The contents of the flask were cooled with dry ice and acetone and the condenser was replaced by a thermometer. The temperature of the mixture was then lowered to -70° ± 2°.and 32 g (0.250 mole) of dried and purified butyl acrylate was added. The polymerization was carried out for 80 hours, 5 ml of methanol was added and the viscous solution was warmed to room temperature. The solvent (toluene) was evaporated at reduced pressure and then at room temperature. To the residue 150 ml of acetone was added, and the polymer solution was poured with stirring into 500 ml of water. The polymer was then redissolved in acetone, reprecipitated with water, and separated. The rubbery polymer was dried under reduced pressure at room temperature. The yield was 6.5 g, 20% of theory.

Preparation of isotactic poly(butyl acrylate) (IV) (80,83,86,89). Toluene (90 ml), dried over calcium hydride and redistilled, was placed in a three-necked flask equipped with a serum cap, a thermometer, and an inlet and an outlet for nitrogen gas. Butyl acrylate (53 ml, 42.4 g, 0.33 mole), dried and distilled under reduced pressure, was added. The mixutre was then cooled to -60° ± 2° and 4.5 ml of 1.6 M n-butyllithium (0.0072 ml) in hexane was injected through the rubber cap. The temperature was then lowered to -70° ± 5° and the mixture was stirred for 6 hours and then held at -70° ± 5° for 72 hours without stirring. To the viscous solution 5 ml of methanol was added and the mixture warmed to room temperature. The solvent (toluene) was evaporated under reduced pressure at room temperature. The polymer was dissolved in 200 ml of acetone and the solution was poured with stirring into 600 ml of water. The rubbery polymer which separated was redissolved in acetone and precipitated again in water. The tacky polymer was taken out and dried under vacuum at room temperature. The yield was 28 g, 66% of theory.

Attempted preparation of isotactic poly(butyl acrylate) (37, 80, 106). A four-necked round-bottomed flask was equipped with an inlet and an outlet for nitrogen gas, a magnetic stirrer, a thermometer, and a graduated addition funnel. One neck of the flask and the addition funnel were fitted with rubber caps. In the flask was placed 262.5 ml (228.4 g) of toluene. Butyl acrylate (21.5 g, 0.168 mole) was placed in the addition funnel. Oxygen was removed from the solvent and the monomer by slowly bubbling a stream of nitrogen through the solution for 2 hours. To the toluene was added with stirring phenylmagnesium bromide (0.012 equiv.) in ether by means of a hypodermic syringe inserted through the serum cap. The mixture was cooled at 0° - 5°. From the addition funnel was added 5 ml of butyl acrylate, and the mixture was allowed to stir at 0° - 5° for 4 hours. The solution was cooled to -70° to -80° by means of a dry ice and acetone bath. The remaining monomer was added dropwise while the temperature was maintained at -70° to -80°. The mixture was stirred for 2 hours and then held at -70° to -80° overnight without stirring. When the solution warmed to room temperature, it was not at all viscous. The mixture did not become viscous even after stirring for three days at room temperature. It was concluded that polymerization had not occurred.

Preparation of syndiotactic poly(butyl acrylate) (V) (1, 27, 28, 75, 99, 106). A three-necked round-bottomed flask was equipped with a magnetic stirrer, a thermometer, and an inlet and an outlet for nitrogen gas. Toluene (58 ml, 50 g), dried and redistilled, was placed in the flask. Butyl acrylate (50 g, 0.39 mole), dried and redistilled, was transferred to the flask. Benzoin (0.42 g, 0.0019 mole), was added to the mixture and the reactants were cooled to -95° (using 1-propanol and liquid nitrogen). The mixture was degassed by bubbling a stream of dry nitrogen through it for 2 hours. During degassing the reactant flask was covered with paper and aluminum foil in order to protect the reactants from the light. The temperature was lowered and maintained at -105° ± 7° before the polymerization was initiated by irradiation with ultraviolet light, produced by a GE.S.4. 100-watt ultraviolet lamp. Nitrogen bubbling and stirring were maintained throughout the reaction. After 8.5 hours of irradiation, the light was turned off, and the reaction mixture allowed to warm to room temperature. The viscous solution was then poured into 200 ml of acetone, the polymer precipitated by pouring into 500 ml of water, and the solid rubbery polymer was separated, redissolved in acetone, and precipitated in water. The polymer was rubbery and white. The yield was 21.5 g, 43% of theory.

Attempted anionic polymerization of dibutyl itaconate (40, 45). Fluorene (0.84 g, 0.005 mole), was placed in a three-necked flask equipped with a thermometer, inlet for nitrogen, and a serum cap and 250 ml of dry redistilled toluene was added. The solution was degassed for 30 minutes and 5 ml of *n*-butyllithium (0.008 mole) in hexane was transferred to the solution. The mixture was stirred for 2 hours at room temperature. It was then cooled to -50° ± 5° and 40 g (0.165 mole) of dibutyl itaconate was added. The polymerization was continued with stirring for 6 hours and kept for another five days without stirring. No change in the viscosity of the solution was noted, indicating that polymerization had not occurred.

Attempted anionic polymerization of dibutyl itaconate (80). Toluene (90 ml), dried and redistilled, was placed in the same apparatus as before. Dibutyl itaconate (40 ml, 39.3 g, 0.162 mole) dried and distilled, was added. The mixture was then cooled to -60° ± 2° and 4.5 ml of a 1.6 *M* solution of *n*-butyllithium (0.0072 mole) in hexane was injected through the rubber cap. The temperature was then lowered to and maintained at -70° ± 5°. The mixture was stirred for 6 hours and was then kept at -70° ± 5° for 77 hours. Since the solution did not get viscous, the mixture was left at room temperature for 6 days more. No viscous solution was obtained and the experiment was abandoned.

Attempted anionic polymerization of dimethyl itaconate (36). Dry toluene (250 ml) was placed in a four-necked flask equipped with a magnetic stirrer, a thermometer, an inlet and an outlet for nitrogen, and a graduated addition funnel. One neck of the flask was fitted with rubber cap. Dimethyl itaconate (18.5 g, 0.117 mole) was charged to the addition funnel, to the solvent was added with stirring 0.012 equiv. of methylmagnesium bromide in ether. The mixture was cooled to 0° - 5°. From the addition funnel was added 5 ml of dimethyl itaconate and the mixture was allowed to stir at 0° - 5° for 4 hours. The solution was cooled to -80° and the remaining monomer was added dropwise while the temperature was maintained at -70° to -80°. The mixture was stirred for 2 hours and was then held at -80° for 52 hours. The solution was not viscous indicating no reaction. The solution was poured into 300 ml of a mixture of methanol, water, and concentrated hydrochloric acid (4:5:1) and the solid monomer that separated was recovered.

Free-radical polymerization of dibutyl itaconate (VI) (57). A three-necked flask equipped with a stirrer, a condenser, a nitrogen inlet, and a thermometer was charged with 25 ml or 24.5 g (0.101 mole) of purified monomer and 35.3 ml of dry benzene. The mixture was heated to reflux under nitrogen and then 0.25 g (0.0015 mole) of 2,2'-azobis(2-methylpropionitrile) was added. Polymerization was allowed to proceed at reflux temperature for 4 days. The solution became very viscous during this time. It was cooled to room temperature and the viscous solution was poured with stirring into 500 ml of water. The polymer collected was dried and redissolved in acetone and precipitated from water. The purified polymer was white, soft and sticky. The yield was 16 g, 65% of theory.

Syndiotactic poly(dibutyl itaconate) (VII) (106). Toluene (58 ml, 50 g), distilled and dried, was placed in a three-necked round-bottomed flask (as in experiment VII). Then dibutyl itaconate (50 g, 0.207 mole), dried and redistilled, was added to the flask. Benzoin (0.42 g, 0.002 mole) was added to the mixture. The reactants were cooled to -95° and oxygen removed by bubbling dry nitrogen through it for 2 hours. The reaction flask was covered with paper and aluminum foil during this treatment, the temperature was lowered to and maintained at $-105^{\circ} \pm 7^{\circ}$ before the reaction was initiated by irradiation with the ultravilet light source, a GE.S.4. 100-watt ultraviolet lamp. Nitrogen bubbling and agitation were maintained throughout the reaction. The irradiation was continued for 10 hours, then the light turned off and the reaction mixture allowed to warm up to room temperature. The reaction mixture was held without stirring at room temperature for 11 days. The highly viscous solution was dissolved in 200 ml of acetone. The polymer was precipitated by pouring the solution into 700 ml of water, and purified as usual. The final purified, dried polymer was white and tacky. The yield was 30.5 g, 61% of theory.

Attempted alkaline hydrolysis of syndiotactic poly(methyl methacrylate) (98). A 20% solution of potassium hydroxide (30 ml) in propanol-water (1:1) was placed in a two-necked flask fitted with a condenser, a separatory funnel and a magnetic stirrer. The flask was heated using a heating mantle. To the hot solution 1.8 g of syndiotactic poly(methyl methacrylate) in 10 ml of toluene was added slowly. The solution was refluxed. After all the polymer had been added, the solution was refluxed for 24 hours. It was then diluted with 30 ml of water, and 20 ml of liquid was distilled from the solution in order to remove the alcohol formed during the saponification. The contents of the flask were refluxed again for 6 hours, then a large excess of hydrochloric acid was added and the mixture was filtered. The polymer was washed with a solution of hydrochloric acid and dried. The NMR spectrum showed no hydrolysis of the polymer.

Attempted alkaline hydrolysis of syndiotactic poly(methyl methacrylate) (34). Syndiotactic poly(methyl methacrylate) (0.5 g) was placed in stainless steel flask equipped with a condenser. Then a 30% solution of potassium hydroxide in 100 ml of ethanol-water (1:1) was added. The solution was refluxed for 7 days and 3 hours. The mixture was cooled to room temperature and enough hydrochloric acid was added to neutralize the base. The solution was filtered. The yellow precipitate was not soluble in water, showing that the amount of hydrolysis was negligible.

Attempted alkaline hydrolysis of syndiotactic poly(methyl methacrylate) (119). Potassium hydroxide (30 ml of 25% solution in water) was placed in the round-bottomed flask equipped with a magnetic stirrer, a condenser, and an addition funnel. The solution was heated to reflux temperature. Syndiotactic poly(methyl methacrylate) (1 g) in 10 ml (toluene) was added dropwise to the hot solution. The mixture was refluxed for 48 hours, then 20 ml of water was added. The alcohol was distilled off and replaced by 10 ml of water. The mixture was refluxed again for 24 hours. The solution was cooled to room temperature and poured into a large excess of hydrochloric acid. The solid polymer which separated was not hydrolyzed as shown by the NMR spectrum.

Attempted acid hydrolysis of syndiotactic poly(methyl methacrylate) (83). Syndiotactic poly(methyl methacrylate) (1 g) was placed in a flask fitted with a condenser. A 57% solution of hydriodic acid (18 ml) was added to the polymer and the solution was refluxed for 52 hours. The mixture was then poured into 100 ml of ice water. The recovered polymer was not hydrolyzed.

Preparation of syndiotactic poly(methacrylic acid) (VIII) (112, 113). Hydrolysis of syndiotactic poly(methyl methacrylate) was tried with 96%, 94%, and 90% sulfuric acid at room temperature. The best results were obtained by the following procedure. The hydrolysis of syndiotactic poly(methyl methacrylate) was carried out by placing 200 ml of sulfuric acid (80%) in a three-necked flask equipped with an inlet and an outlet for nitrogen, and a magnetic stirrer. Poly(methyl methacrylate) (8 g) was added to the acid. The solution was stirred until the polymer dissolved (2 hours). Then the flask was placed in a water bath at 40° - 50° for 170 hours. After the reaction was complete the hydrolyzate was poured into 3 liter of ice-water mixture and the precipitate that formed was filtered off. The precipitate was dissolved in a sodium hydroxide solution and reprecipitated with hydrochloric acid. The precipitate was washed with dilute hydrochloric acid and dried. A white powder was obtained. The yield was 5.5 g or 80% of theory.

Preparation of isotactic poly(methacrylic acid) (IX) (46, 55, 76). The hydrolysis of isotactic poly(mehtyl methacrylate) was carried out by placing 250 ml of sulfuric acid (80%) in a round-bottomed flask equipped with a thermometer, and an inlet and an outlet for nitrogen. The polymer (7 g) was added and the mixture was stirred for 3 hours until the polymer was dissolved. The flask was then placed in a water bath at 30° - 50° for 175 hours. The hydrolyzate was poured into a 3 liters of ice-water mixture and the poly acid was filtered. The purification was performed by redissolving the poly acid in sodium hydroxide solution and precipitating in acid solution. The hydrolyzed polymer was white and powdery. The yield was 3.8 g, 63% of theory.

Attempted hydrolysis of isotactic poly(butyl acrylate) (46, 55). Isotactic poly(butyl acrylate) (0.5 g) was placed in a flask, then 50 ml of sulfuric acid (96%) was added. The mixture was stirred at room temperature for 6 days. The solution was poured into 50 g of crushed ice and the precipitate that formed was filtered out. The filtered polymer was dark but partially hydrolyzed. Different sulfuric acid concentrations (80% and 70%) were also tried under nitrogen atmosphere in a water bath at 40° - 50°. Although partial hydrolysis of polymer occurred, the polymeric acid was dark in color and the degree of hydrolysis could not be improved enough to make the polymeric acid water soluble.

Attempted hydrolysis of isotactic poly(butyl acrylate) (86, 88, 89). Isotactic poly(butyl acrylate) (1 g) was placed in a flask equipped with a magnetic stirrer and a condenser. The polymer was then suspended in 45 ml of 20% of hydrochloric acid. The mixture was refluxed for 6 days, and the solution was poured into 150 ml of ice-water. Filtered polymer was not soluble in water and the NMR spectrum indicated no hydrolysis.

Attempted hydrolysis of isotactic poly(butyl acrylate) (60). Isotactic poly(butyl acrylate) (1 g) was dissolved in 50 ml of acetic acid and water (4:1), p-toluenesulfonic acid (0.2 g) was added as a catalyst, and the solution was refluxed for 161 hours. During this period most of the butyl acetate formed by transesterification was removed by distillation. The product was isolated by pouring the solution into a large amount of crushed ice (300 g). Partial hydrolysis was achieved by this method, but the resulting polymer was not soluble in water.

Attempted solvolysis of isotactic poly(butyl acrylate). A mixture of acetic acid (150 ml) and trifluoroacetic acid (5 ml) was placed in a flask and 12 drops of concentrated sulfuric acid was added. The mixture was refluxed for 198 hours. The hot solution was cooled and poured into a large excess of crushed ice. The isolated polymer was not acetolyzed as shown by its lack of solubility in water.

Attempted solvolysis of isotactic poly(butyl acrylate) (60). Isotactic poly(butyl acrylate) (1.5 g) was dissolved in a mixture of 40 ml of acetic acid and 40 ml of trifluoroacetic acid and the solution was refluxed for 120 hours. After each 24 hours the butyl acetate formed, if any, was removed by distillation and replaced with acetic acid. After 120 hours the mixture was poured into crushed ice. The isolated polymer was found to be not acetolyzed as evidenced by its low solubility in water.

Attempted solvolysis of isotactic poly(butyl acrylate). Acetic acid (88.5 ml) was poured into a flask, then 15 ml of phosphoric acid (86%) was added. Isotactic poly(butyl acrylate) was dissolved in the solution and the mixture was refluxed for 265.5 hours. The solution was then poured into an excess of ice. The filtered polymer was slightly soluble in water, indicating partial reaction.

Hydrolysis of isotactic poly(butyl acrylate) (X). Isotactic poly(butyl acrylate) (9 g) was placed in a round-bottomed flask equipped with a condenser and a magnetic stirrer. The polymer was then dissolved in a mixture of acetic acid (367 ml) and concentrated hydrochloric acid (133 ml). The solution was refluxed for 384 hours. The hot mixture was poured into an excess of crushed ice. The solid collected after filtration was dried and ground to a slightly colored powder. The yield was 4.8 g, 95% of theory.

Preparation of syndiotactic poly(acrylic acid) (XI). The hydrolysis of syndiotactic poly(butyl acrylate) was carried out by placing 367 ml of acetic acid and 133 ml of concentrated hydrochloric acid in a round-bottomed flask equipped with a condenser and a magnetic stirrer, to which 10 g of poly(butyl acrylate) was added. The mixture was refluxed for 480 hours. The solution was then poured into an excess of ice. The solid collected after filtration was dried and ground to a fairly white powder. The yield was 4.7 g, 83.5% of theory.

Attempted hydrolysis of poly(dibutyl itaconate). The hydrolysis of poly-

(dibutyl itaconate) was carried out by placing 60 ml of sulfuric acid (70%) in a three-necked flask. Poly(dibutyl itaconate) (1 g) was added to the acid. The solution was stirred under nitrogen atmosphere for 16 hours until the polymer dissolved. Then the flask was placed in a water bath at 30° - 40° for 139.5 hours. The hydrolyzate was poured into an ice-water mixture. The separated polymer was somewhat soluble in water, but the color was slightly dark. Sulfuric acid (97%) was also tried but again the product was not hydrolyzed enough to be soluble in water.

Attempted solvolysis of poly(dibutyl itaconate). Poly(dibutyl itaconate) (1 g) was dissolved in 100 ml of glacial acetic acid. Trifluoroacetic acid (5 ml) was added as a catalyst and the solution was refluxed for 120 hours. Butyl acetate produced during the solvolysis was removed by distillation every 24 hours. The polymer was precipitated by pouring it into water. The product was slightly soluble in water, but the desired extent of reaction could not be obtained by this method.

Solvolysis of poly(dibutyl itaconate) (XII). A mixture of acetic acid (500 ml) and trifluoroacetic acid (35 ml) was placed in a round-bottomed flask equipped with a condenser. Then 15 drops of concentrated sulfuric acid was added. Poly(dibutyl itaconate) (10 g) was dissolved in the solution. The mixture was refluxed for 21.3 days. Then the solution was poured into an excess of crushed ice. The poly acid was washed with dilute hydrochloric acid and dried. A white powder was obtained. The yield was 5.3 g, 99% of theory.

Infrared Spectroscopic Studies of Polymers

The infrared spectra of the polymers were obtained via potassium bromide pellets and thin films on a sodium chloride plate. The films were initially dried from the solvent by evaporation in a vacuum desiccator for 3 hours. The phases used for preparation of polymer samples are summarized in Table VII.

Nuclear Magnetic Resonance Studies of Polymers

A solution of 15% (w/v) was prepared for each polymer in a suitable solvent. Tetramethylsilane (TMS) was used as a reference standard either externally or internally. The solvent and the method of using the TMS standard are summarized in Table VIII.

Potentiometric Titrations of Poly Acid Solutions

Poly acid solutions were prepared by dissolving about 0.05 g of polymer in 10 ml of standard 0.1 N sodium hydroxide solution. Standard hydrochloric acid was added slowly to the mixture with magnetic stirring. Potential readings were made after each addition of 0.25 to 0.5 ml. The temperature was kept at 23 $\pm$ 0.1 C$^{\circ}$.

Determination of Number-Average Molecular Weights of Polymers

The determinations were performed with a Hitachi Perkin-Elmer Coleman 115 with dry acetone as the solvent. The main oven temperature of the instrument was set at 40° and the sub-oven temperature at 32°.

A calibration curve was made by using different concentrations of benzil in acetone. Since the calibration curve was linear and passed

TABLE VII

THE PHASES USED FOR DETERMINING INFRARED SPECTRA OF POLYMER SAMPLES

Polymer	Film	Pellet
I	-	KBr
II	-	KBr
IV	CCl_4	-
V	CCl_4	-
VII	CCl_4	-
VIII	-	KBr
IX	-	KBr
X	-	KBr
XI	-	KBr
XII	-	KBr

TABLE VIII

CONDITIONS FOR NMR STUDIES OF POLYMERS

Polymer	Solvent	TMS
I	C_6H_5Cl	Internal
II	C_6H_5Cl	Internal
IV	C_6H_5Cl	Internal
V	C_6H_5Cl	Internal
VII	C_6H_5Cl	Internal
VIII	D_2O	External
IX	D_2O	External
X	D_2O	External
XI	D_2O	External
XII	D_2O	External

through the origin, the instrument was ready for molecular weight measurements of the polymers. Solutions of polymers were made by dissolving polymers in dry acetone to make 2% solution. Five readings were taken for each solution and the readings averaged. The molar concentrations of the polymer solutions were determined from the calibration curve of benzil in acetone.

Determination of Toxicity

Six male Swiss mice weighing at least 17 g each were used in each experiment. Treatment consisted of a single intraperitoneal injection of polymer solution. The volume injected was calculated from the weight of the mouse and the concentration of the polymer solution in order to give each mouse the desired dose level in mg/kg. After 4 days, mortalities were recorded. At this time the surviving mice were weighed again and sacrificed. The dose level was varied until the dose causing a mortality rate of 50% was determined. This was recorded as the LD_{50}. Any Any change in weight was noted. A loss of weight indicated toxicity. Results are given in Table IX.

The single dose required to kill 50% of the mice varies from 40-90 mg/kg for most polymers tested. The LD_{50} for syndiotactic poly(methacrylic acid) is particularly large, being greater than 1600 mg/kg. The low toxicity of this polymer may be due to its low molecular weight since toxicity is less for polymers of low molecular weight. However, the possibility that its low toxicity is related to its particular steric configuration cannot be overlooked.

TABLE IX

LD_{50} OF POLYMERS FOR SWISS MICE

Compound	Dose mg/kg	Average Weight Change On Fourth Day, g
Isotactic Poly(methacrylic acid)	40	-1.2
Syndiotactic Poly(methacrylic acid)	1600	-1.3
Isotactic Poly(acrylic acid)	80	-4.2
Syndiotactic Poly(acrylic acid)	70	-0.2
Poly(itaconic acid)	90	-1.0

CHAPTER IV

RESULTS AND DISCUSSIONS

Twelve polymers have been prepared from acrylic, methacrylic, and itaconic esters; these are listed in Table X.

Many theories have been proposed in regard to the propagation steps of free-radical and anionic polymerizations. Although some of these theories conflict, they have not been either disproved or generally accepted because of lack of sufficient experimental evidence. One of the most important and fundamental concepts required for considering the reaction mechanism is whether or not monomer double bonds open stereoselectively in free-radical or anionic polymerization.

A rapid attack of anionic initiator on the monomer occurs (22, 40, 128), but in some cases the attack is indiscriminate and takes place on both olefinic and carbonyl double bonds (45). A high mole percent of low molecular weight by-product is thus produced (42). The proportion of low molecular weight by-products including alkoxides (or their precursors) is dependent on the initiator. Both steric hindrance and carbanion stability increases the initiator selectivity (123, 126), e.g., butyllithium < fluorenyllithium < 1,1-diphenylhexyllithium.

Another substantial proportion of the growing chains is believed to become "pseudo-terminated" (41), perhaps by forming a cyclic intermediate which propagates only reluctantly, as in Figure 4. In addition to pseudo-terminated chains, a smaller fraction produces a propagating

TABLE X

POLYMERS PREPARED

Polymer Number	Polymer	Experiment Number
I	Isotactic Poly(methyl methacrylate)	2
II	Syndiotactic Poly(methyl methacrylate)	3
III	Isotactic Poly(butyl acrylate)	4
IV	Isotactic Poly(butyl acrylate)	5
V	Syndiotactic Poly(butyl acrylate)	7
VI	Poly(dibutyl itaconate)	11
VII	Poly(dibutyl itaconate)	12
VIII	Syndiotactic Poly(methacrylic acid)	17
IX	Isotactic Poly(methacrylic acid)	18
X	Isotactic Poly(acrylic acid)	25
XI	Syndiotactic Poly(acrylic acid)	26
XII	Poly(itaconic acid)	29

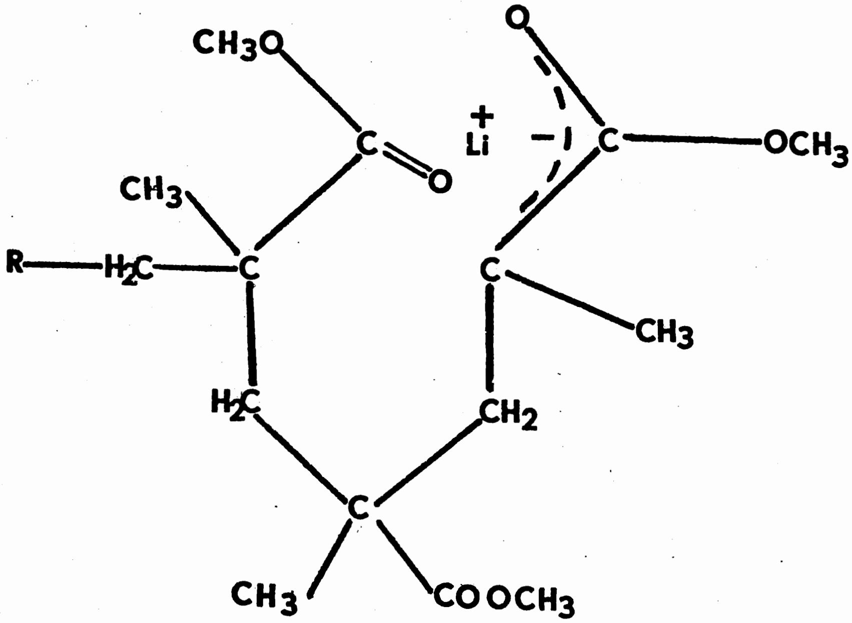


Figure 4. "Pseudo-termination" by Forming a Cyclic Intermediate.

structure which continues to add units rapidly in isotactic placement to form a high polymer. With suitable precautions, termination can be avoided. As a result of these complex processes, even though initiation is rapid and all units remain "living", they do not all grow at the same rate and a wide molecular weight distribution results even in highly isotactic systems (107) $[\bar{M}_V/\bar{M}_N = 7 - 18]$.

Alkoxides and ethers (127) tend to compete with monomer for cation and complex reaction kinetics result. Their presence also results in a change in stereoregularity from isotactic to stereoblock sequences.

A study by Yoshino and co-workers showed that anionic polymerization of deuterated methyl acrylate by lithium aluminum hydride led to a single definite mode of opening (131) which he later established as trans (threo-meso or isotactic-like approach) (132). Shortly there-after, Yoshino demonstrated that the mode of approach of anion to monomer was very sensitive not only to the initiator used but also to any added solvent such as ether. Qualitatively, then, it appears that conditions which alter the configurations of α-carbon atom from isotactic to stereoblock sequences also alter the direction of approach of anion to monomer and the configuration of the β-carbon atom. Furthermore, the β-carbon atom configuration is more sensitive to changes in reaction condition than the α-configuration. The most profound differences in α- and β-tacticity between polymers produced under different conditions can be related to the counterion, the ratio of Lewis base (diethyl ether or tetrahydrofuran) to initiator, and the temperature during polymerization. Whenever two monomers are polymerized under nearly identical conditions, the one with the larger ester function produces the higher proportion of erythromeso structures. This result suggests that bulkier ester function favor a syndiotactic-like approach (30). Branching has only a small effect on the isotacticity, except for tert.-butyl methacrylate. This polymer gave rise to the lowest degree of isotacticity observed for any of the polymers.

Most of the common polymerization techniques have been applied to the various itaconic derivatives. Free radical initiation is accomplished by peroxides of varying thermal stabilities. The lower reaction temperatures result in higher polymer molecular weight. Azobisisobutyronitrile is an effective initiator in nonaqueous systems, while persulfate salts are useful for polymerization in emulsion. Radiation initiation has been observed in dimethyl itaconate homopolymerization by gamma rays from a ^{60}Co source (54).

Several attempts to initiate anionic polymerization of itaconic derivatives, such as esters and bis(N,N-dimethyl)itaconamide, have produced no polymer (66, 79, 97) although isomerization of mesaconate occured (79). While strong bases may cause extensive isomerization, free radicals apparently do not.

The higher dialkyl itaconates which have been investigated show an increase both in polymerization rate and intrinsic viscosity with increasing size of the alkyl group in bulk polymerization. Part of the rise in rate observed in proceeding from dimethyl to higher dialkyl itaconates is due to decreasing rate of termination which results from the increase in viscosity of the esters in the order: ethyl < butyl < octyl. Initiator concentration does not have a pronounced effect on molecular weight in itaconate polymerization.

The major infrared (IR) absorption regions of polymer I-XII are summarized in Table XI. Characteristic bands (1725-1765 cm^{-1}) for the carbonyl group are found for all polymers. The O-H stretching bands in the 3300 to 2900 cm^{-1} region are found in the case of poly acids. This band usually overlays the C-H stretching region and is typical of carboxylic acid. Some acid anhydride is found to be present in acrylic and methacrylic acids (85). This agrees with the spectrum of dehydrated poly(methacrylic acid) which indicates that a great majority of the anhydride is cyclic (35). These facts show that poly(acrylic acid) is converted to anhydride as easily as the isotactic methacrylic acid (81, 82). No change in stereoregularity was found after hydrolysis.

Much work has been done using NMR for investigation of stereoregularity (14-17, 31). Bovey and Tiers (13) were the first to make use of NMR to determine the tacticity of poly(methyl methacrylate), and they obtained their spectra from polymers dissolved in chloroform in sealed

TABLE XI

INFRARED ABSORPTION SPECTRA (IN cm^{-1}) OF POLYMERS I-XII

II	III	V	VII	XII	XVII	XVIII	XXV	XXVI	XXIX	Assignment*
-	-	-	-	-	3350	3350	2950	3320	3330	O-H
2910	2950	2900	2910	2950	2950	2940	2860	2875	2990	C-H
		2850	2850	2860				3050		
1712	1740	1725	1728	1735	1685	1690	1665	1685	1715	C-O
-	-	-	-	-	865	-	880	-	890	O-H bending
1420	1450	1450	1448	1452	1440	1440	1428	1430	1430	CH_2 bending
1130	1170	1160	1158	1175	1165	1160	1135	1140	1180	C-O-C Symmetry
1380	1350	1330	1310	1340	1270	1370	-	-	-	C-O-C Asymmetry

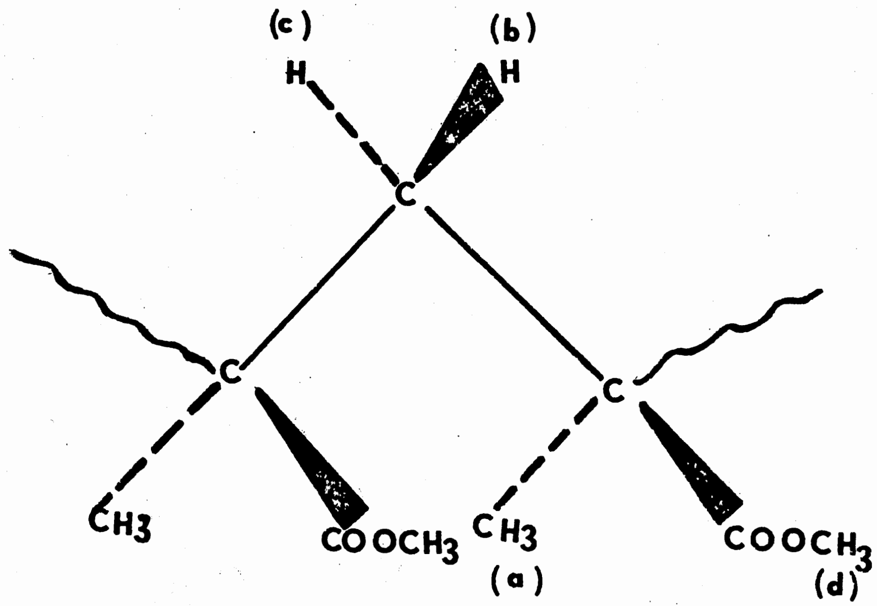
---

*Stretching frequencies unless otherwise marked tubes at 90°. It was noted, however, that resolution could be improved by taking the spectra in o-dichlorobenzene at elevated temperature (100). The nuclear magnetic resonance of poly(methyl methacrylate) shows this fact. The methylene protons resonance in predominantly syndiotactic polymers is a singlet as expected, although somewhat broad and complicated by the residual isotactic fraction. The methylene protons in isotactic poly(methyl methacrylate) give the expected quartet with the additional peak due to syndiotactic sequences. The peak due to the α-substituent does not by itself provide an absolute indication of configuration. The chemical shifts of α-substituents commonly vary appreciably with the relative configuration of the nearest neighboring monomer units, but this is not always the case. In the expanded spectrum of poly(methyl methacrylate) Bovey and Tiers (13) found that the resonance of the α-methyl protons (δ 0.7-1.3) does not result in a single peak as expected but gives three different peaks. These three peaks were assigned to the α-methyl protons appearing in isotactic, heterotactic, and syndiotactic triads. The assignment of the signals in the NMR spectra of isotactic and syndiotactic poly(methyl methacrylate) in chlorobenzene are summarized in Tables XII and XIII.

Backbone methylene protons (e and f) of isotactic poly(butyl acrylate) produced two quintets; one at δ 1.75 - 2.00 and the other δ 2.04 - 2.46. The methine proton (d) shows a quintet centered at δ 2.65. The analysis of the theoretical NMR spectrum (80, 82) has shown that the first two quintets correspond to non-equivalent protons of the methylene group and that they do not overlap each other. According to Yoshino *et al.* (132), the absorption peaks ranging from δ 1.75 - 2.00 are due to isotactic methylene proton trans to the carbonyl groups, and those from

TABLE XII

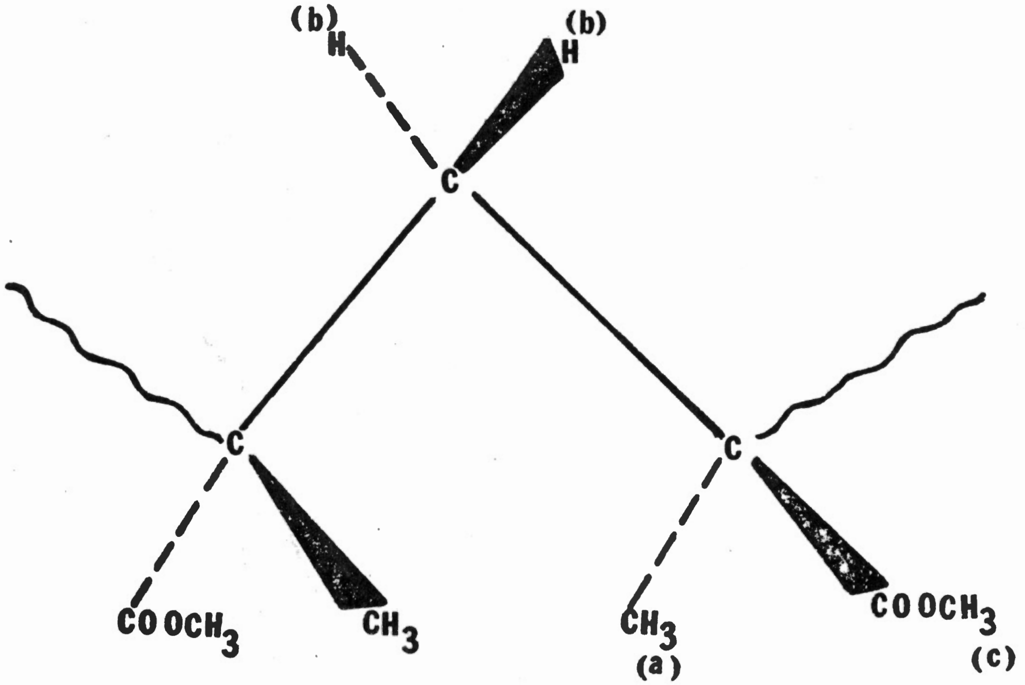
THE PROTON MAGNETIC RESONANCE SPECTRUM AND PEAK ASSIGNMENT OF POLYMER I



Chemical Shift,δ	Description	Integration	Assignment
1.1-1.3	Singlet, Broad	3	H_a
2.2-2.5	Doublet	1	H_b
1.5-1.76	Doublet	1	H_c
3.4-3.7	Singlet	3	H_d

TABLE XIII

THE PROTON MAGNETIC RESONANCE SPECTRUM AND PEAK ASSIGNMENT OF POLYMER II



Chemical Shift, δ	Description	Integration	Assignment
0.9-1.3	Singlet, Broad	3	H_a
1.8-2.16	Singlet	2	H_b
3.3-3.7	Singlet	3	H_c

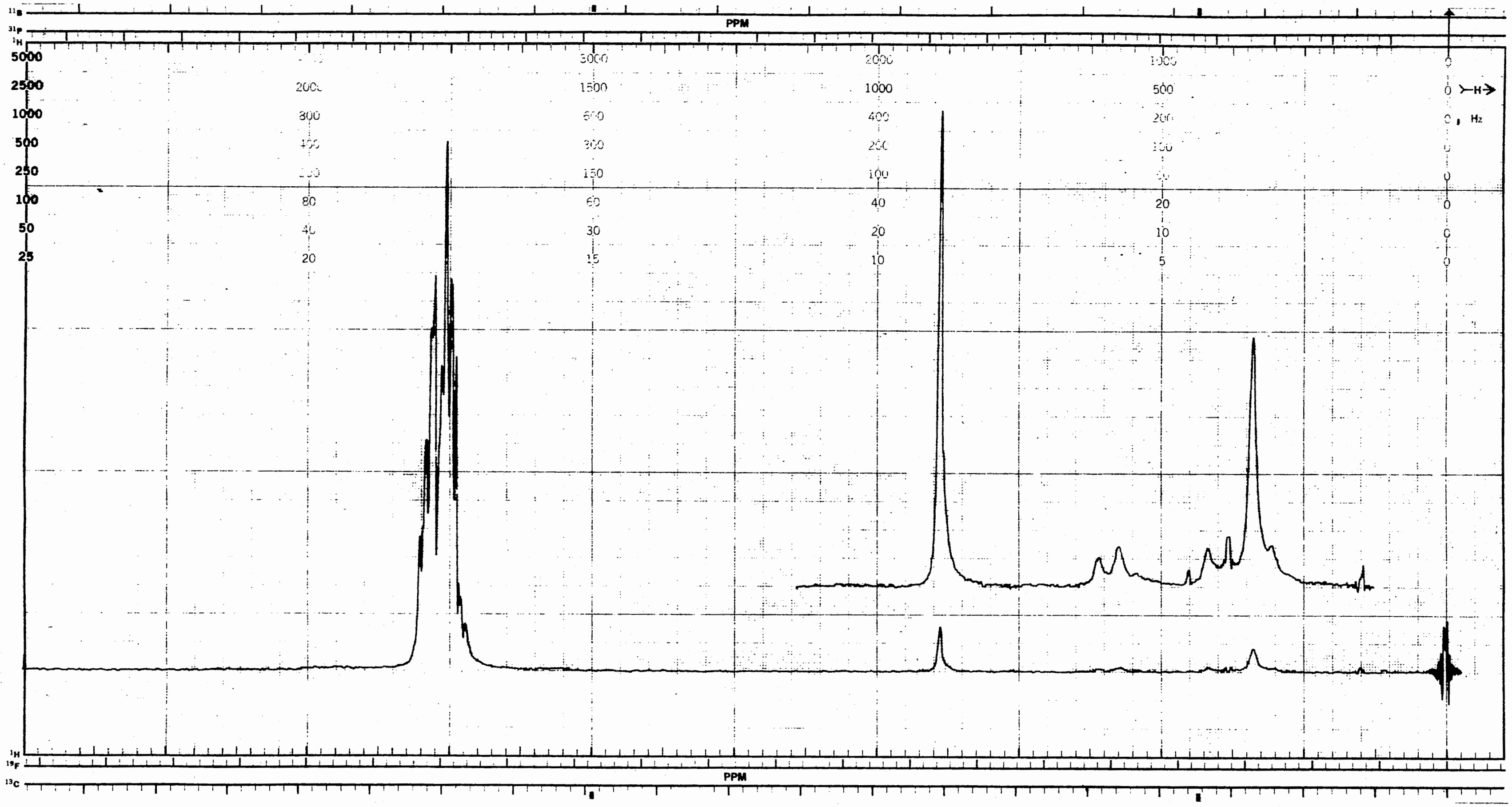


Figure 5. Proton Magnetic Resonance of Isotactic Poly(methyl methacrylate)(I) - 100 MHz

R. F. 56 dB	S. W. 1000 Hz	S. A. 1.0
F. B. 2 Hz	S. T. 250 Sec	S. O. 83701 Hz

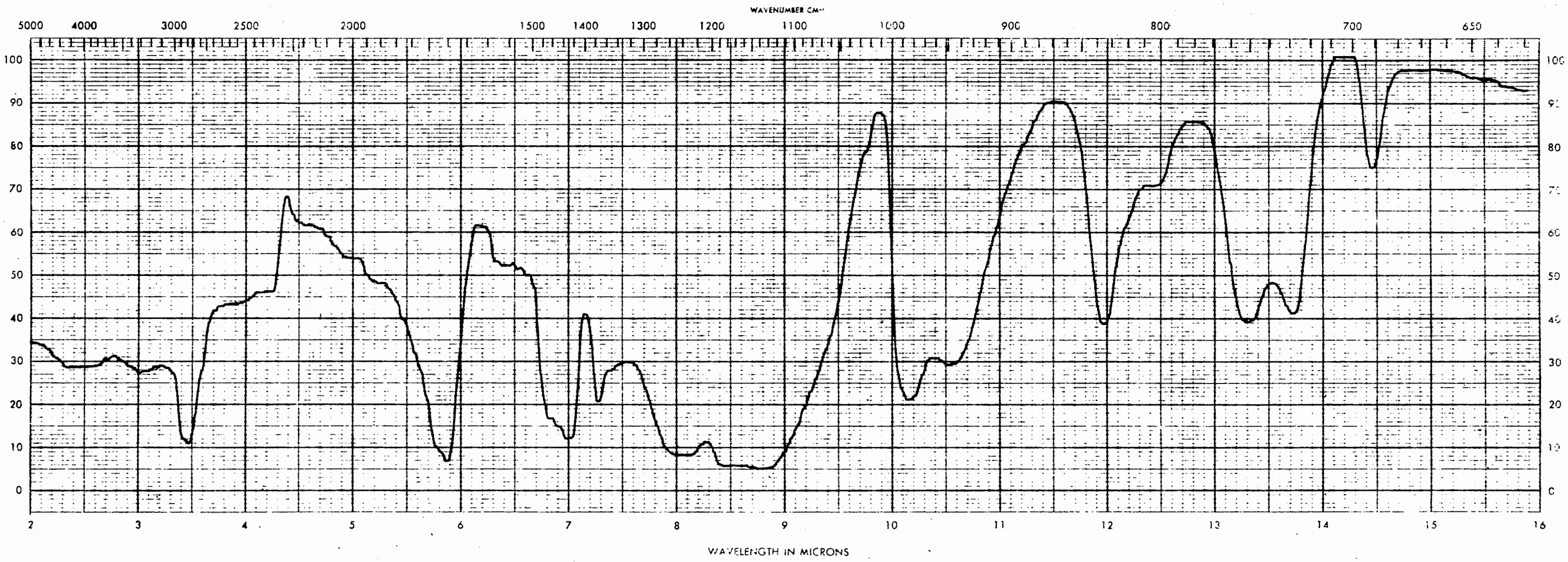


Figure 6. Infrared Spectrum of Isotactic Poly(methyl methacrylate)(I), KBr Pellet

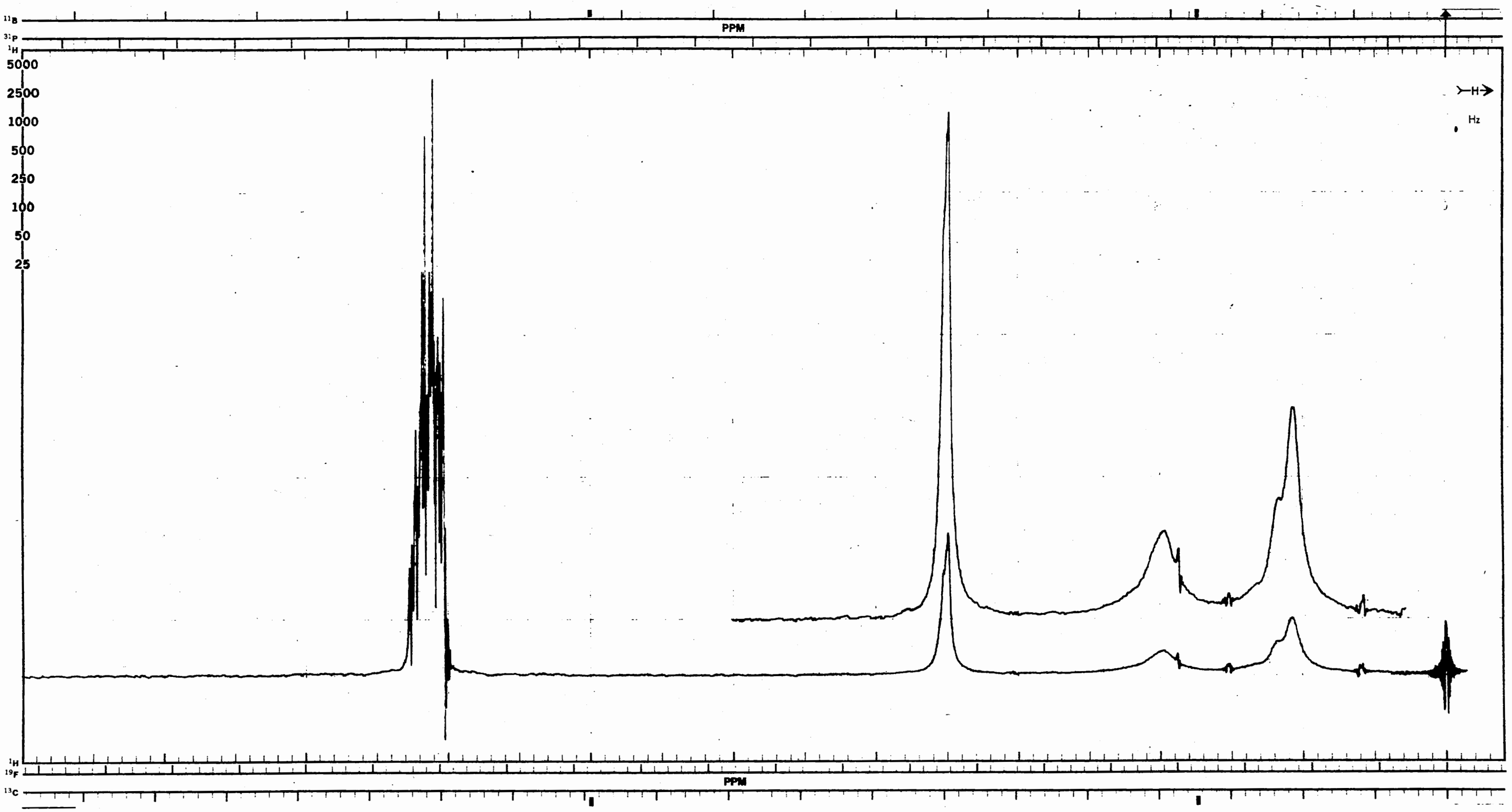


Figure 7. Proton Magnetic Resonance of Syndiotactic Poly(methyl methacrylate)(II) - 100 MHz

R. F. 57 dB	S. W. 1000 Hz	S. A. 1.0
F. B. 2 Hz	S. T. 250 Sec	S. O. 83701 Hz

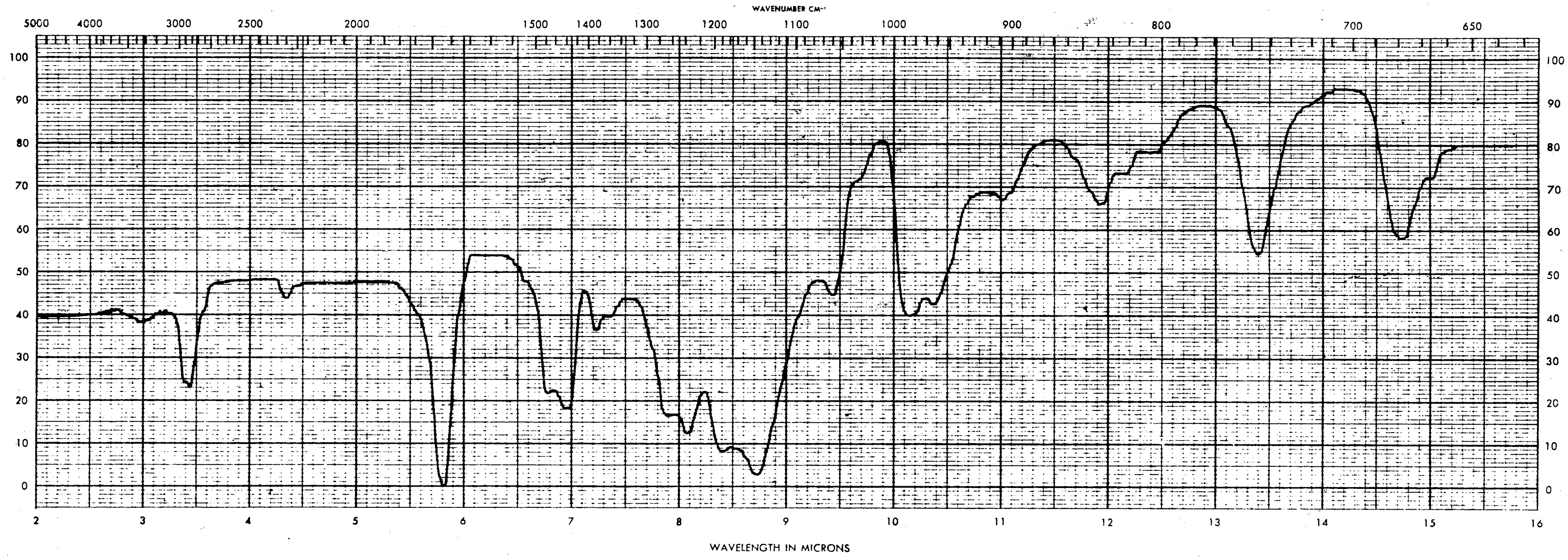


Figure 8. Infrared Spectrum of Syndiotactic Poly(methyl methacrylate)(II), KBr Pellet

δ 2.04 - 2.46 are due to the one with the gauche conformation. The spectrum of syndiotactic poly(butyl acrylate) shows a multiplet at δ 1.76 - 1.96 due to methylene protons, together with weak absorption at δ 2.06 - 2.30. Absorption due to the methine proton is similar to that of isotactic poly(butyl acrylate) and shows a multiplet at δ 2.4 - 2.8.

The assignment of the signals in the NMR spectra of isotactic and syndiotactic poly(butyl acrylate) in chlorobenzene is summarized in Tables XIV and XV. NMR spectrum of poly(dibutyl itaconate) shows a triplet at δ 0.7 - 1.1 due to the methyl group in the butyl chain and another triplet at δ 3.8 - 4.3 due to the methylene group attached to oxygen. The other methylene groups show absorption at δ 1.2 - 1.9. Peaks due to the methylene group attached to -C = O are centered at δ 2.9.

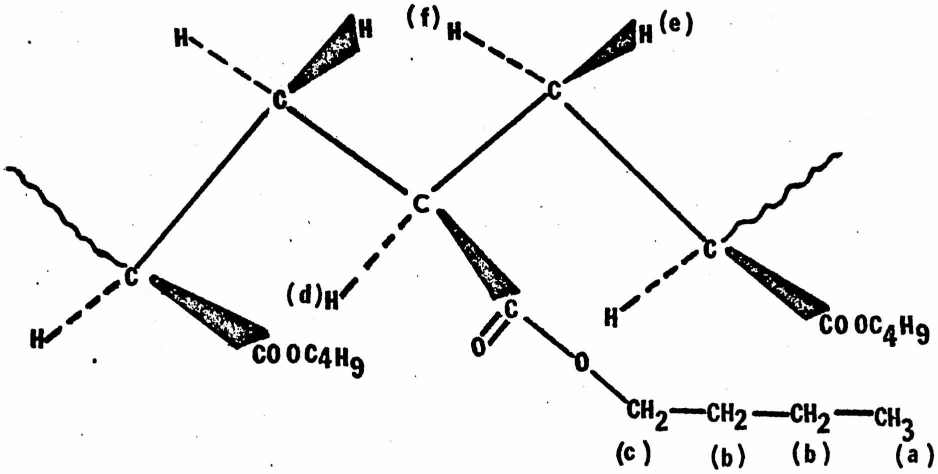
The nature of methylene splitting is an absolute measure of the predominant configuration of the polymers. The isotacticities of poly(butyl acrylate) and poly(methyl methacrylate) were calculated by comparing the area of backbone methylene peaks in isotactic polymer with the total area in isotactic and syndiotactic polymers. From the ratio of area under the peak due to isotactic polymer to that under the peaks of syndiotactic and isotactic polymers the fraction of isotactic configuration is estimated.

In a similar way, the fraction of syndiotactic configuration is found from the ratio of the peak area due to syndiotactic to the total area. These values are tabulated in Table XVI.

The number-average-molecular weights of polymers I, II, IV, V, VI and VII were determined using the Hitachi Perkin Elmer Coleman 115 Molecular Weight apparatus by measuring the vapor pressure difference

TABLE XIV

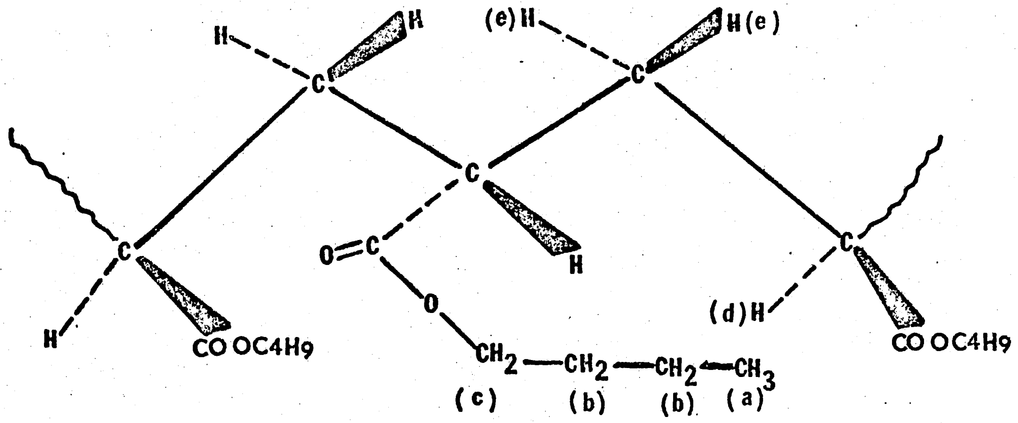
THE PROTON MAGNETIC RESONANCE SPECTRUM AND PEAK ASSIGNMENT OF POLYMER IV



Chemical Shift, δ	Description	Integration	Assignment
0.70-1.00	Triplet	3	H_a
1.10-1.68	Multiplet	4	H_b
3.98-4.24	Triplet	3	H_c
2.46-2.80	Quintet	1	H_d
2.00-2.40	Quintet	1	H_e
1.70-1.90	Quintet	1	H_f

TABLE XV

THE PROTON MAGNETIC RESONANCE SPECTRUM AND PEAK ASSIGNMENT OF POLYMER V



Chemical Shift, δ	Description	Integration	Assignment
0.90-1.02	Triplet	3	H_a
1.14-1.76	9 Peaks	4	H_b
4.00-4.24	Triplet	3	H_c
2.40-2.80	Multiplet	1	H_d
1.76-1.96	Multiplet	2	H_e

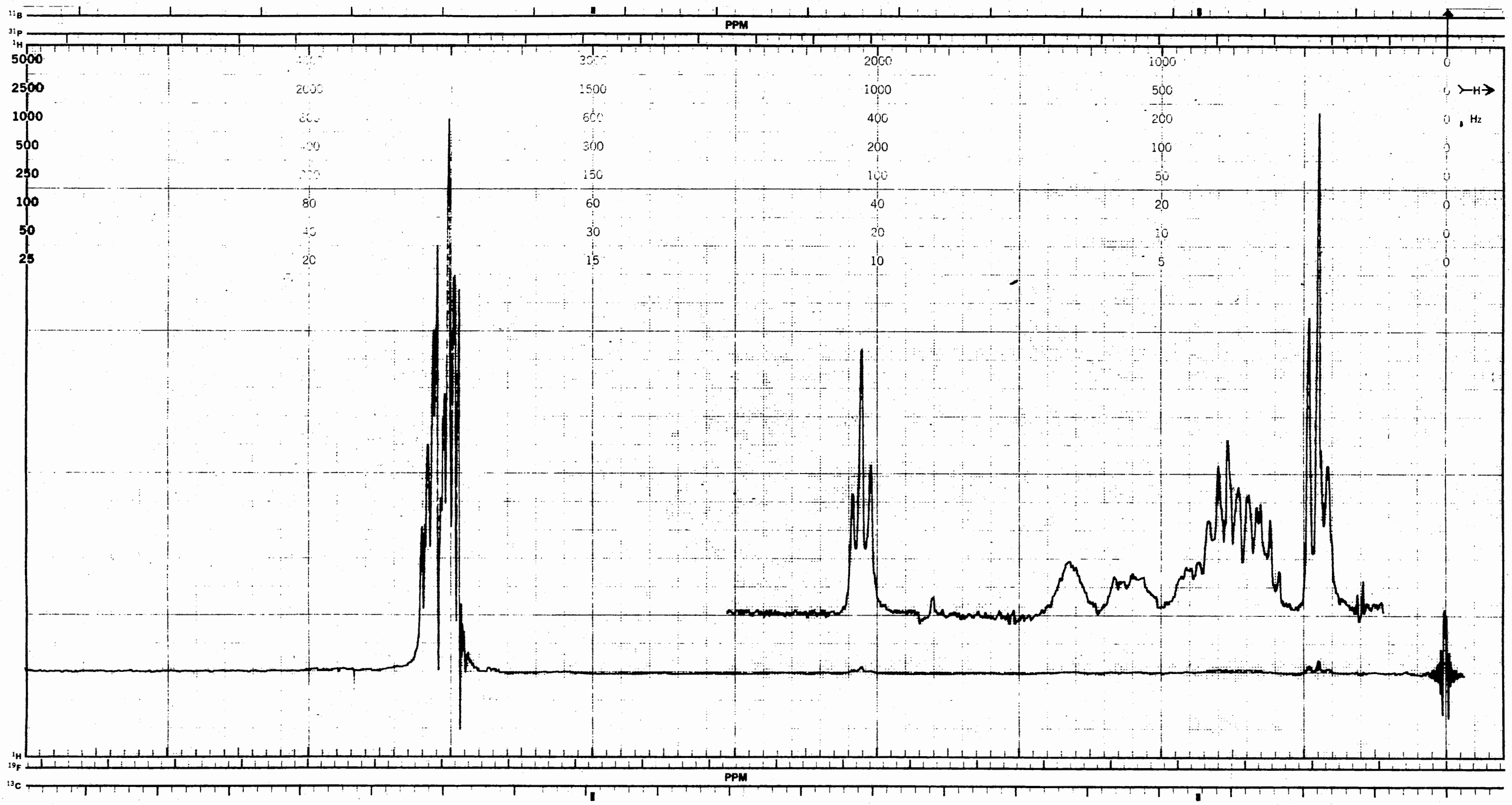


Figure 9. Proton Magnetic Resonance of Isotactic Poly(butyl acrylate)(IV) - 100 MHz

R. F. 55 dB
F. B. 2 Hz

S. W. 1000 Hz
S. T. 250 Sec

S. A. 1.0
S. O. 83701 Hz

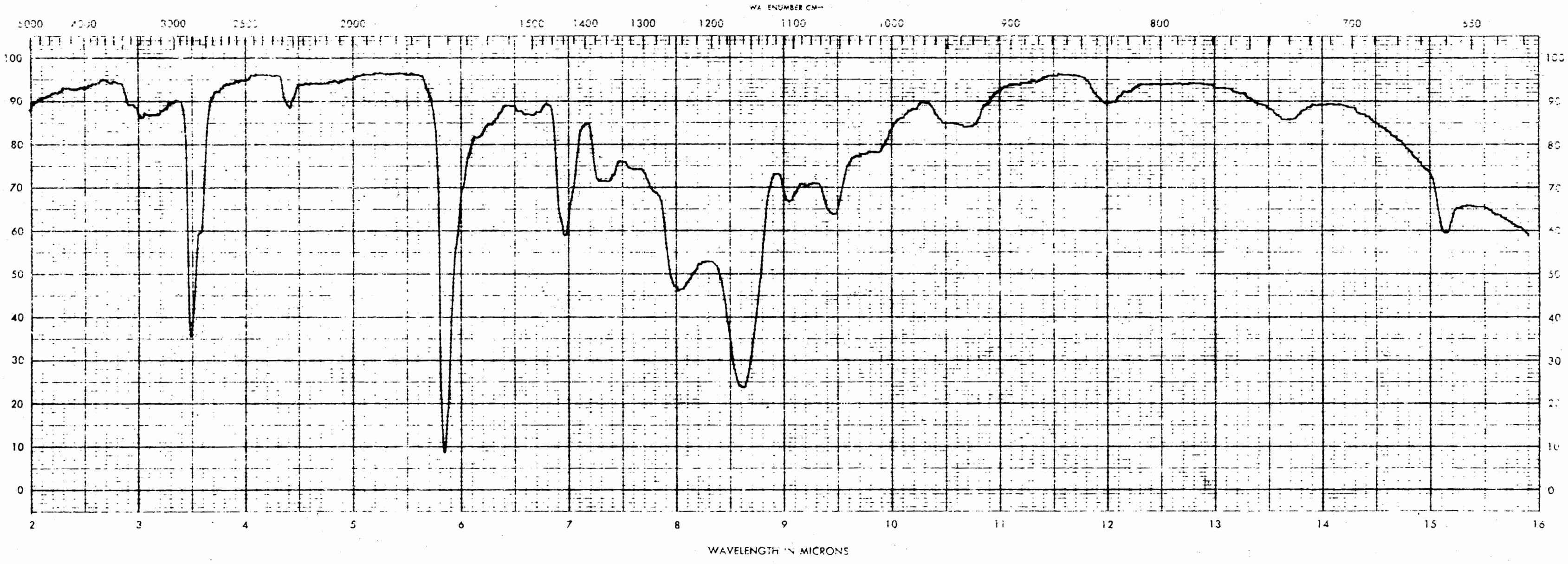


Figure 10. Infrared Spectrum of Isotactic Poly(butyl acrylate)(IV) - Film on Sodium Chloride Plates

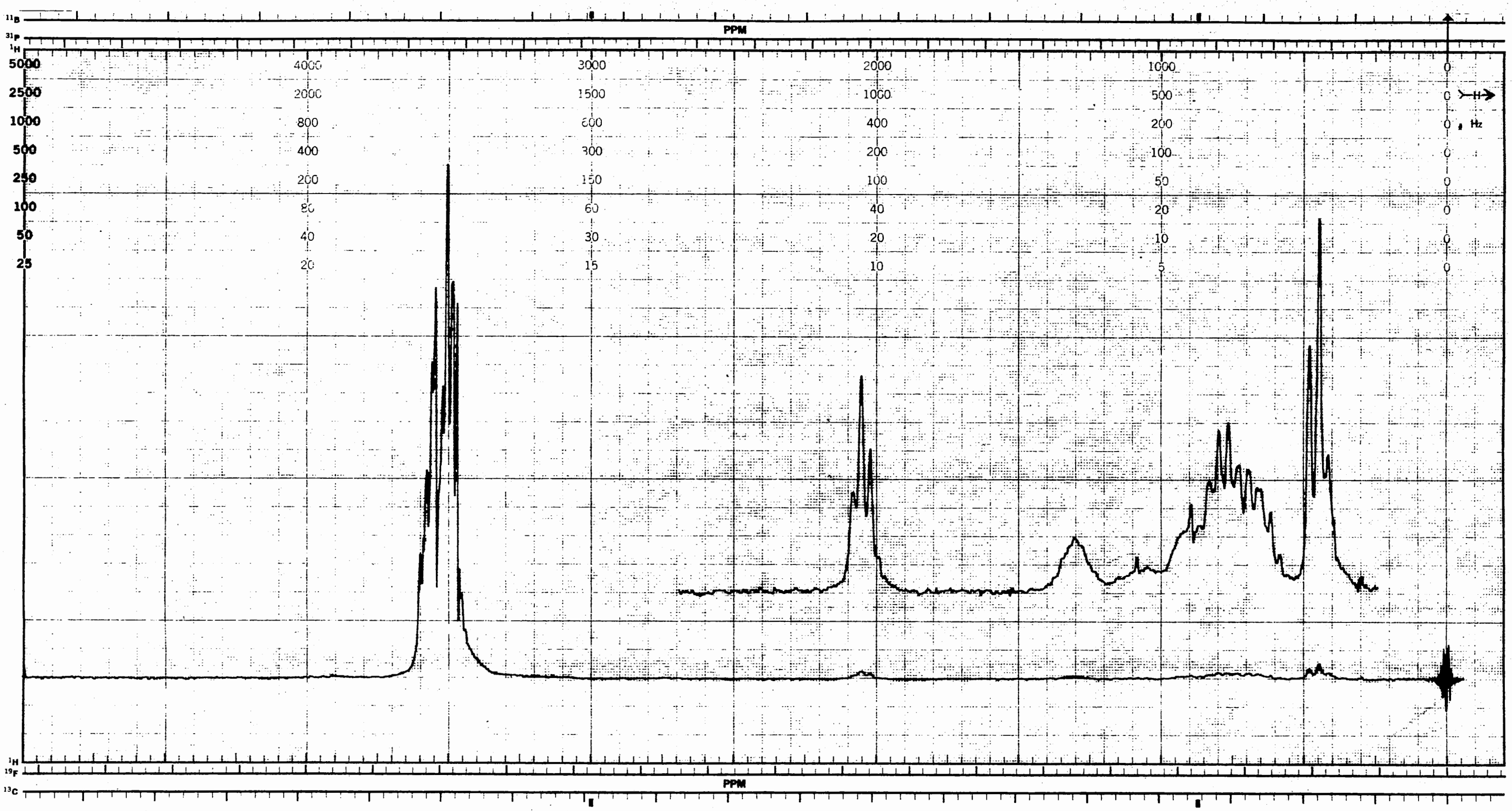


Figure 11. Proton Magnetic Resonance of Syndiotactic Poly(butyl acrylate)(V) - 100 MHz

R. F. 56 dB
F. B. 2 Hz

S. W. 1000 Hz
S. T. 250 Sec

S. A. 1.0
S. O. 83701 Hz

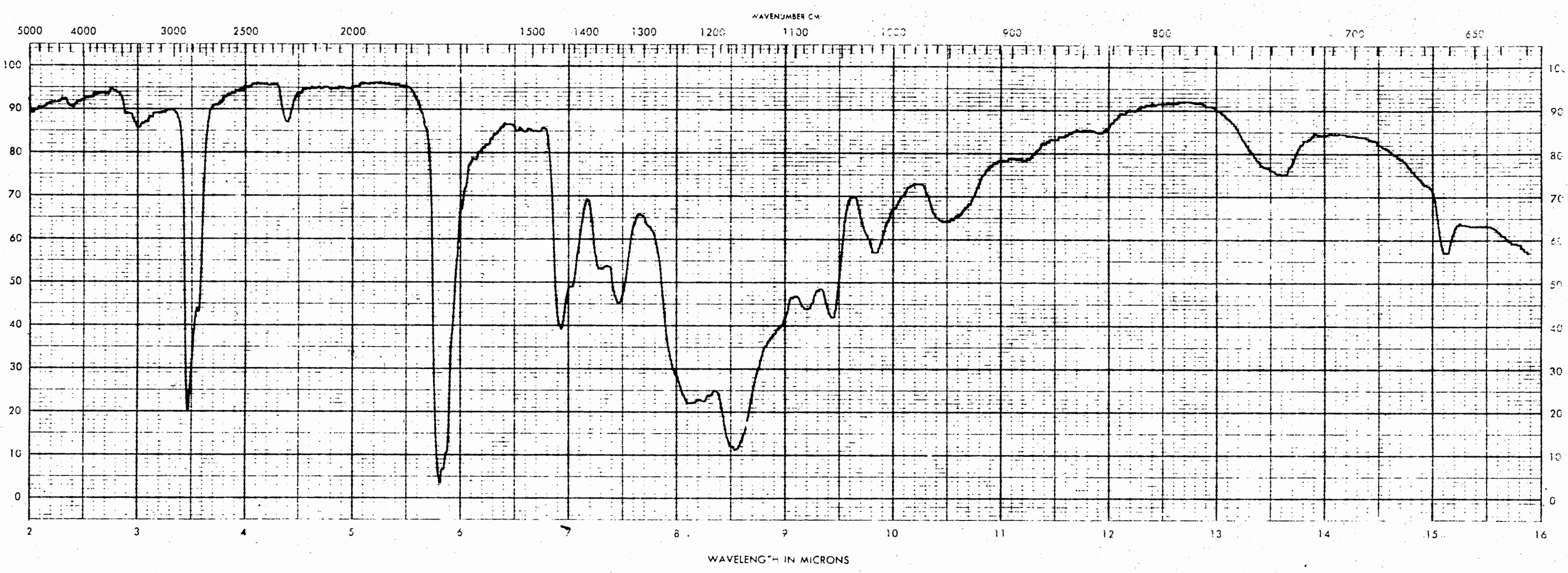


Figure 12. Infrared Spectrum of Syndiotactic Poly(butyl acrylate)(V) - Film on Sodium Chloride Plates

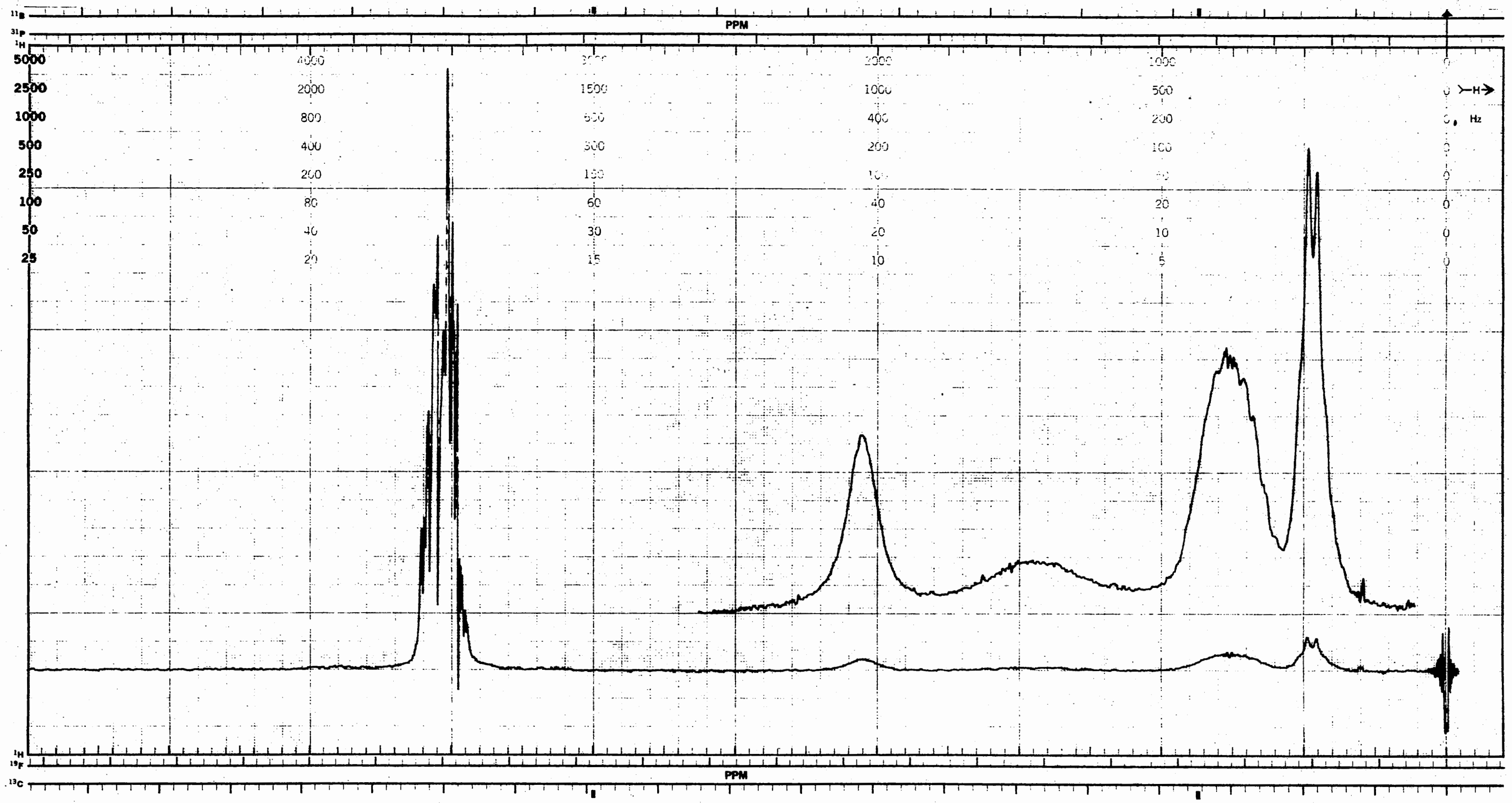


Figure 13. Proton Magnetic Resonance of Poly(dibutyl itaconate)(VII) - 100 MHz

R. F. 55 dB	S. W. 1000 Hz	S. A. 1.25
F. B. 2 Hz	S. T. 250 Sec	S. O. 83701 Hz

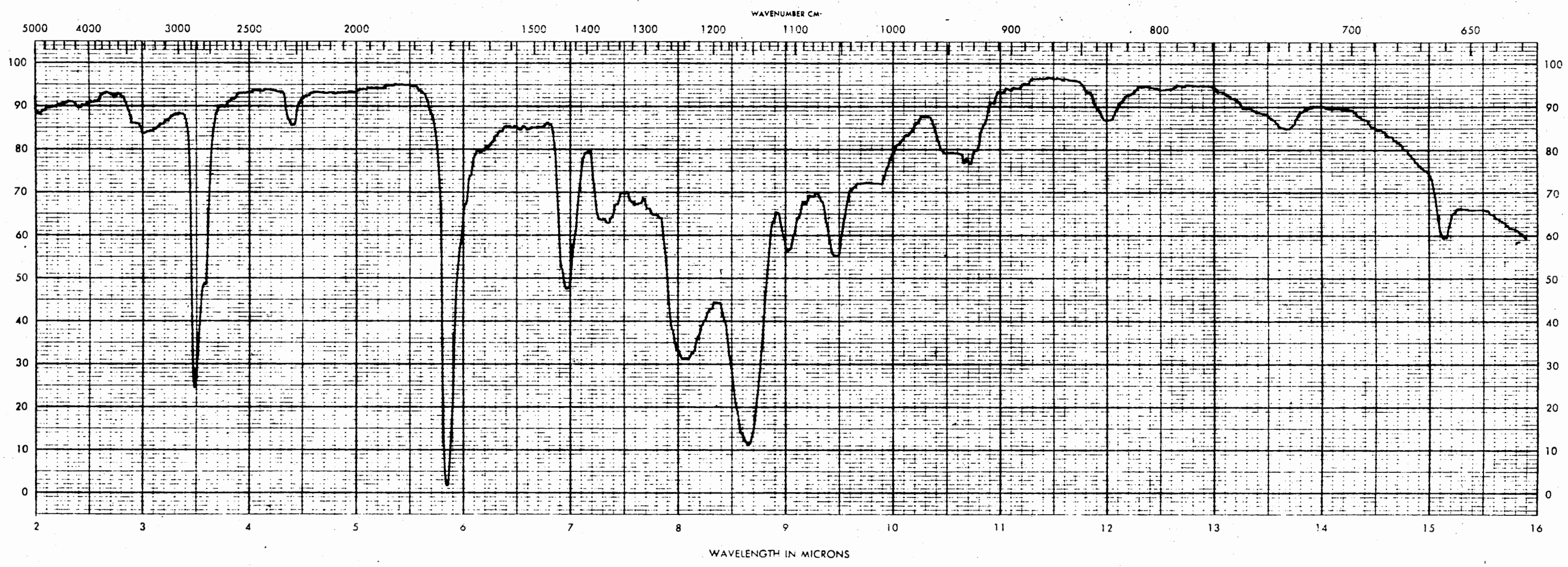


Figure 14. Infrared Spectrum of Poly(butyl itaconate)(VII) - Film on Sodium Chloride Plates

TABLE XVI

STEREOREGULARITY IN POLY(METHYL METHACRYLATE)(I AND II) AND POLY(BUTYL ACRYLATE)(IV AND V)

Polymer	Initiator	Solvent	% Isotactic	% Syndiotactic
Poly(methyl methacrylate)	9-fluorenyllithium	Toluene	97	3
Poly(methyl methacrylate)	9-fluorenyllithium	Tetrahydrofuran	83	17
Poly(butyl acrylate)	n-butyllithium	Toluene	92	8
Poly(butyl acrylate)	Benzoin, uv	Toluene	27	73

between the solvent and the solution. The results are shown in Table XVII.

Several studies have been recently reported in which the rates of homogeneous hydrolysis of methacrylate (91) and acrylate (20, 108) polymers have been measured. The kinetics observed follow no simple behavior, and it has been proposed (92) that the rate of hydrolysis of a given ester group is affected by the configuration of the groups proximate to it. The different conformations which the isotactic and syndiotactic polymers may assume can be the predominant source of difference in chemical reactivity. It was reported (81, 82) that isotactic poly(methyl methacrylate) forms an anhydride on acid hydrolysis more easily than does syndiotactic or atactic polymers. During hydrolysis, the carbonyl groups in isotactic polymers can approach each other, on the other hand, in syndiotactic polymers, they are apart perhaps due to a zig-zag conformation. The poly(methacrylic acid) produced by hydrolysis could be esterified to give poly(alkyl methacrylate) with the same tacticity (36).

Glavis (39) reported some results concerning the alkaline hydrolysis of poly(methyl methacrylate) of various tacticities. He showed that syndiotactic polymers hydrolyze relatively slowly, while the hydrolysis of isotactic polymer proceeds rapidly and to a higher final conversion than syndiotactic polymer. It was implicitly admitted that the tacticity of polymeric chain remains unchanged in the course of the hydrolysis. Matsuzaki and Ishida (83) examined the stability of carbon-hydrogen bond during the hydrolysis. They claimed racemized product both in acid and alkaline hydrolysis.

The NMR spectra of the polymeric acids VIII, IX, X, XI and XII

TABLE XVII

NUMBER-AVERAGE-MOLECULAR WEIGHT OF POLYMERS

Polymer	$\bar{M}_N$
Isotactic Poly(methyl methacrylate)	10800
Syndiotactic Poly(methyl methacrylate)	5400
Isotactic Poly(butyl acrylate)	15200
Syndiotactic Poly(butyl acrylate)	52600
Poly(dibutyl itaconate)[a]	11900
Poly(dibutyl itaconate)[b]	5100

[a] Benzoin, u.v. initiated

[b] Free-radical initiated

were recorded from approximately 15% (w/v) solution in D_2O with TMS as an external standard. The Klesper method (69, 70) was used to calculate the degree of hydrolysis.

The peak due to $-OCH_3$ (δ 3.4 - 3.7) in the spectra of isotactic and syndiotactic poly(methacrylic acid) vanished drastically, but there is no change in the peak due to $-CH_3$ (δ 0.8 - 1.4) or CH_2 (δ 1.6 - 1.9). The triplet peak corresponding to $-OCH_2$ (δ 4.4 - 4.24) in poly(butyl acrylate) also disappeared in the spectra of isotactic and syndiotactic poly(acrylic acid). Since this region is very close to the absorption of H-OD, the determination was made based on the decrease in peak area due to the methyl portion of the butyl group (δ 0.7 - 1.0) which also completely disappeared in poly(acrylic acid) spectrum. The percentage of hydrolysis of the different polymers is summarized in Table XVIII.

Potentiometric Titration

The potentiometric titration curves of atactic, isotactic and syndiotactic poly(methacrylic acid) have been obtained in the presence of various concentrations of sodium chloride (90). The values of pH + log $[(1-\alpha)/\alpha]$ for the isotactic form are always higher than those of syndiotactic, that is, it requires greater work to remove proton from the former than from the latter. The difference between the two stereoregular poly acids may be accounted for by assuming that the isotactic poly(methacrylic acid) has a "locally" helical structure in solution. There are qualitative differences in the potentiometric titration behavior of poly(methacrylic acid) and poly(acrylic acid). The differences seem to be due to a difference in the over-all chain flexibility.

A carboxylic acid in aqueous solution dissociates as

TABLE XVIII

HYDROLYSIS OF POLYMERS

Polymer	Extent of Hydrolysis %
Isotactic Poly(methacrylic acid)	96
Syndiotactic Poly(methacrylic acid)	97
Isotactic Poly(acrylic acid)	96
Syndiotactic Poly(acrylic acid)	99
Poly(itaconic acid)	74

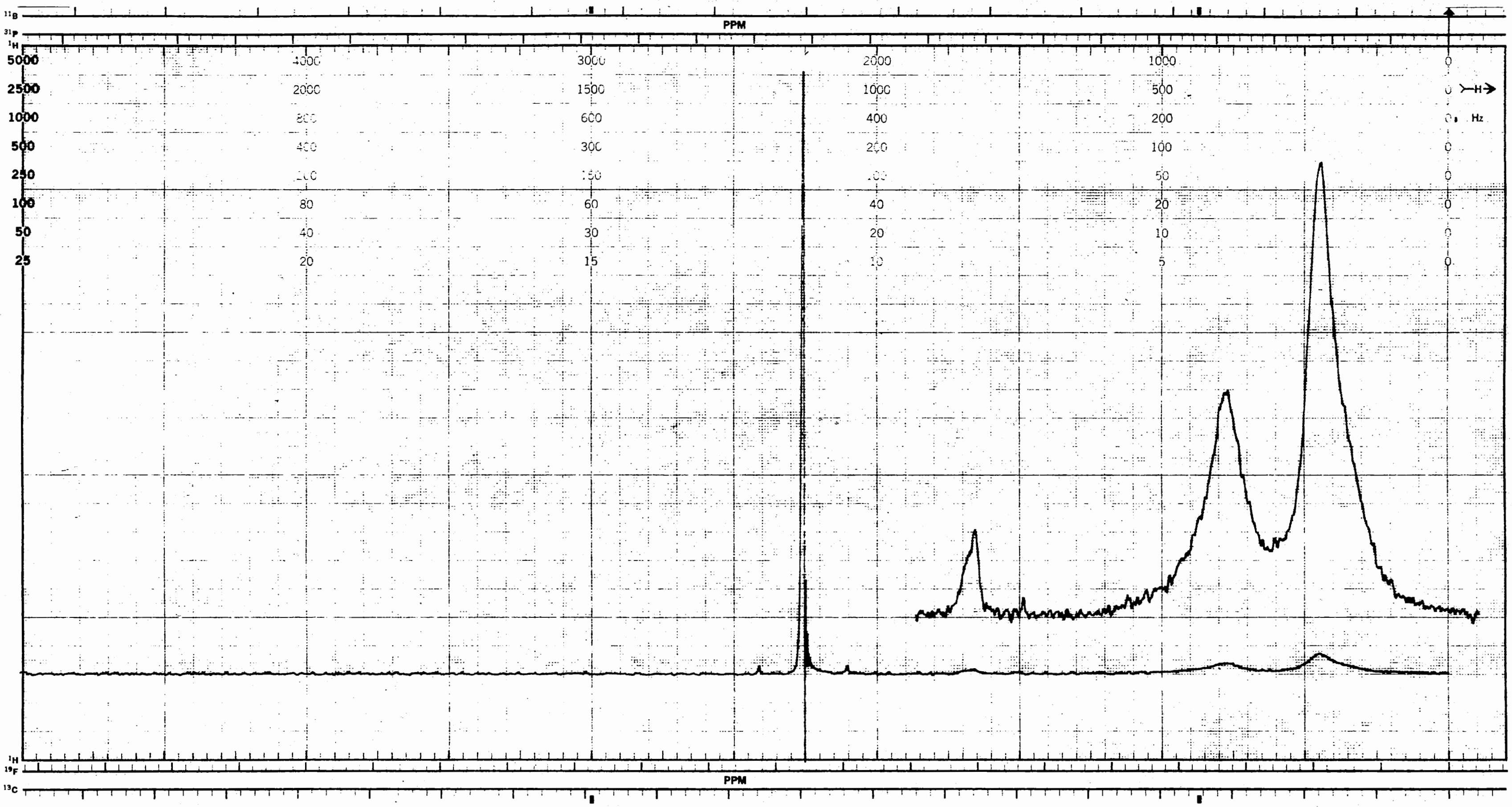


Figure 15. Proton Magnetic Resonance of Isotactic Poly(methacrylic acid)(IX) - 100 MHz

R. F. 64 dB	S. W. 1000 Hz	S. A. 1.25
F. B. 2 Hz	S. T. 250 Sec	S. O. 83477 Hz

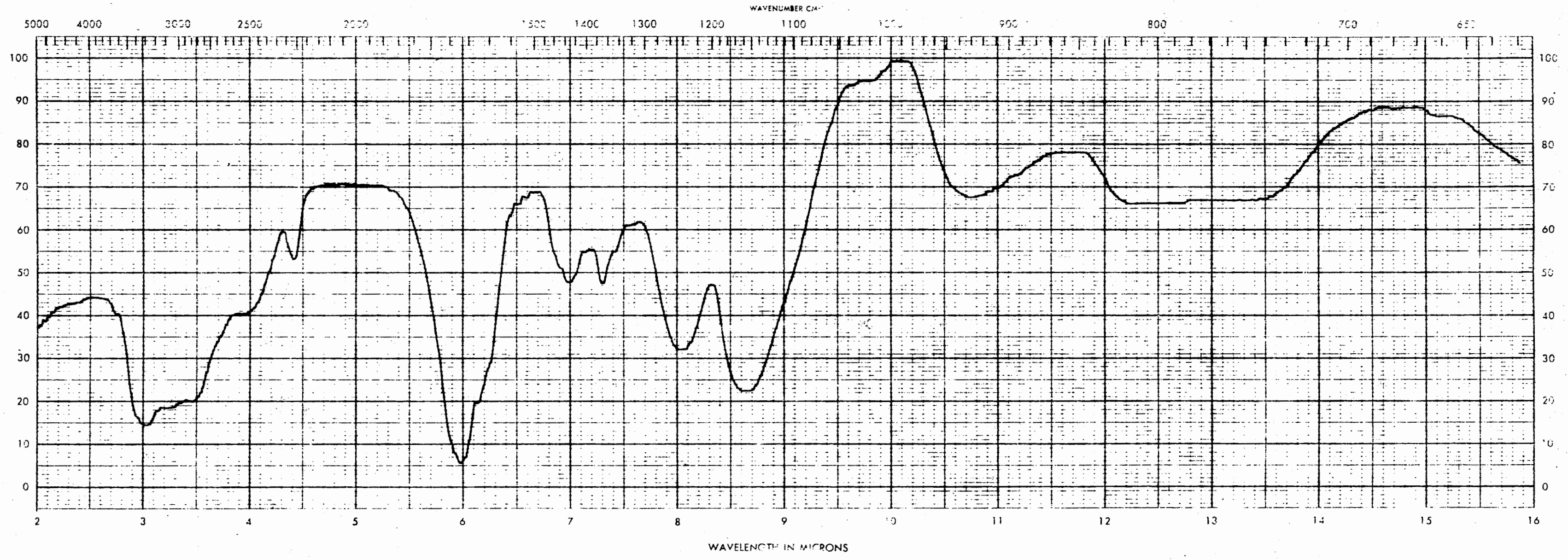


Figure 16. Infrared Spectrum of Isotactic Poly(methacrylic acid)(IX), KBr Pellet

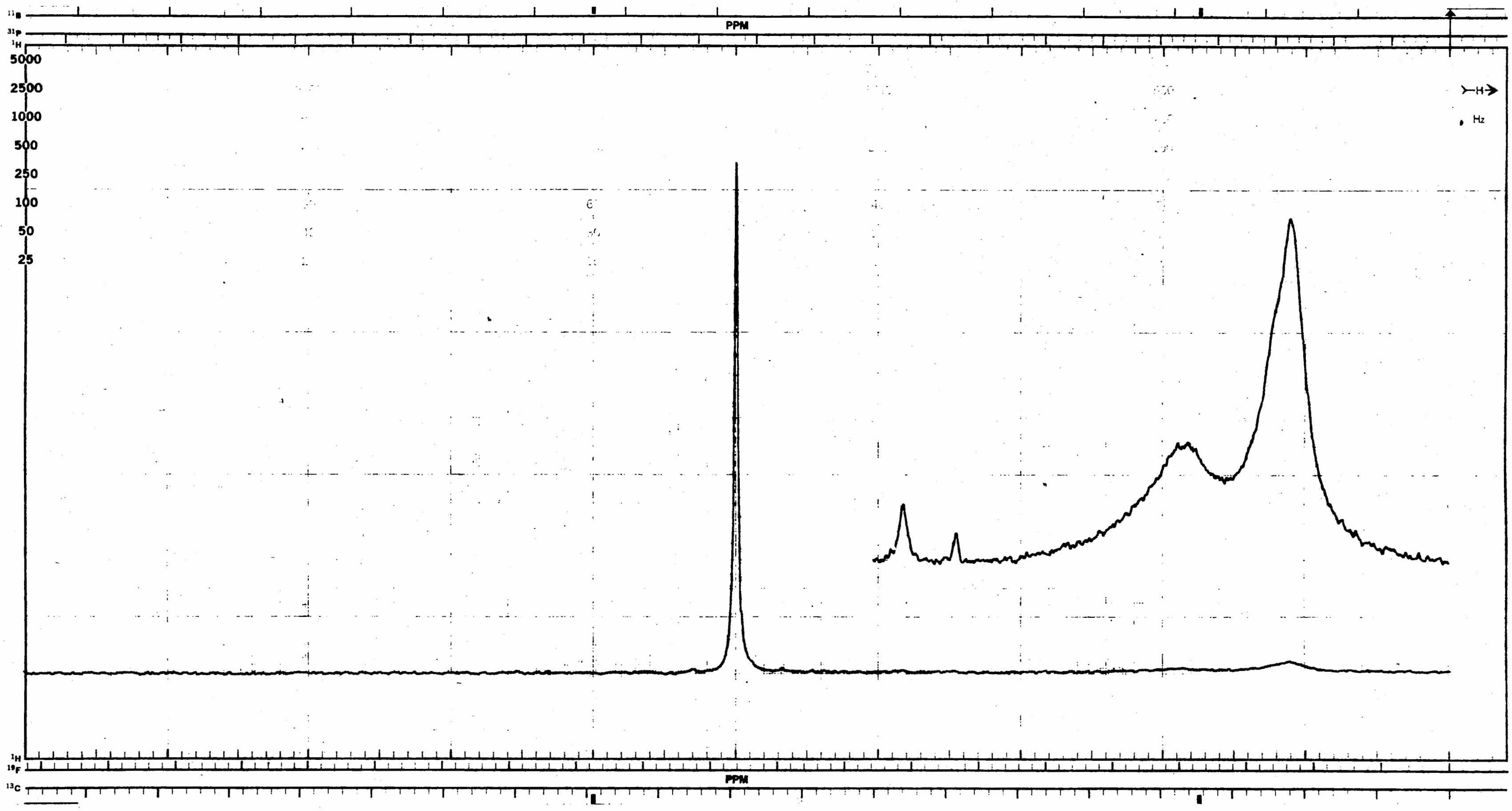


Figure 17. Proton Magnetic Resonance of Syndiotactic Poly(methacrylic acid)(VIII) - 100 MHz

R. F. 60 dB	S. W. 1000 Hz	S. A. 1.0
F. B. 2 Hz	S. T. 250 Sec	S. O. 83151 Hz

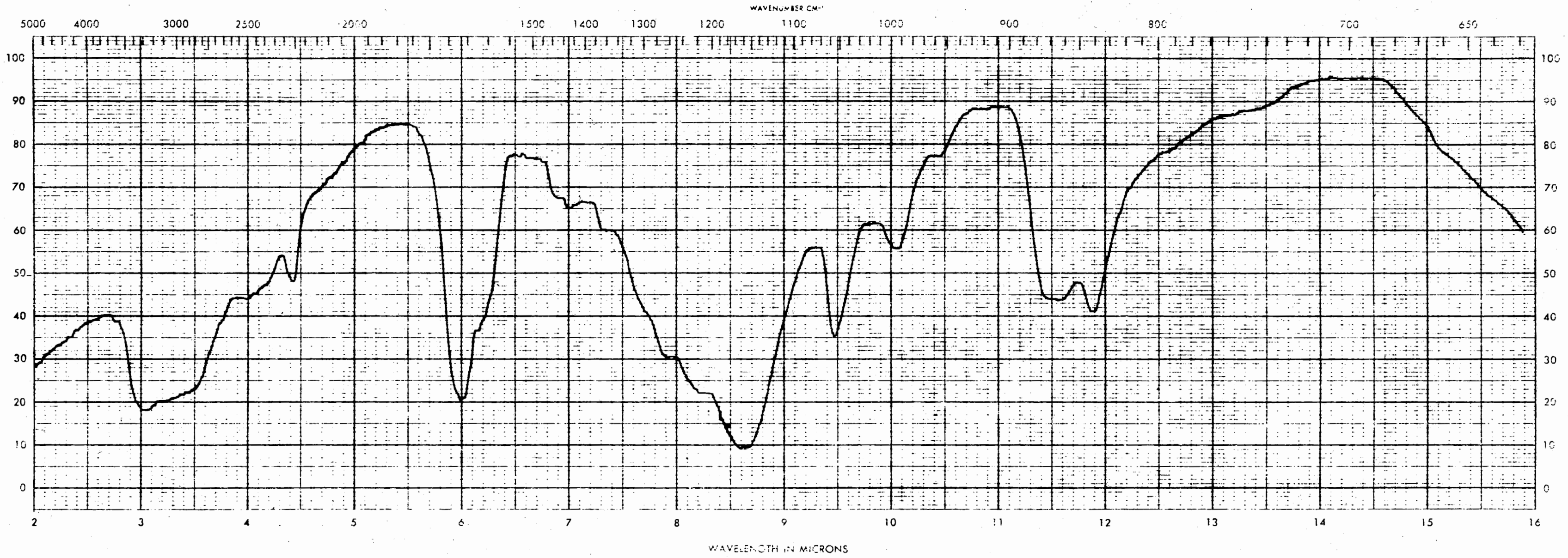


Figure 18. Infrared Spectrum of Syndiotactic Poly(methacrylic acid)(VIII), KBr Pellet

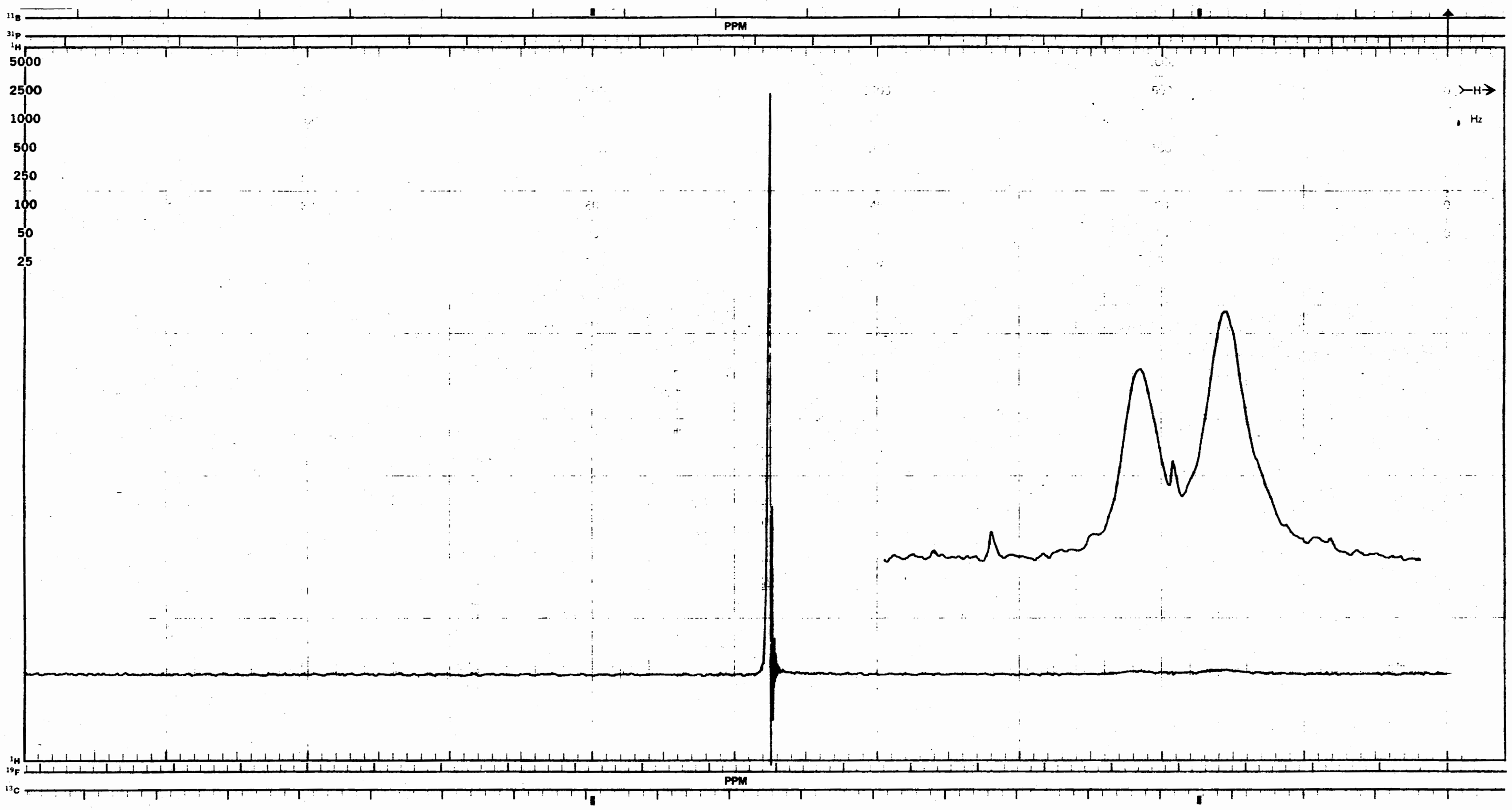


Figure 19. Proton Magnetic Resonance of Isotactic Poly(acrylic acid)(X) - 100 MHz

R. F. 54 dB	S. W. 1000 Hz	S. A. 1.25
F. B. 2 Hz	S. T. 250 Sec	S. O. 83131 Hz

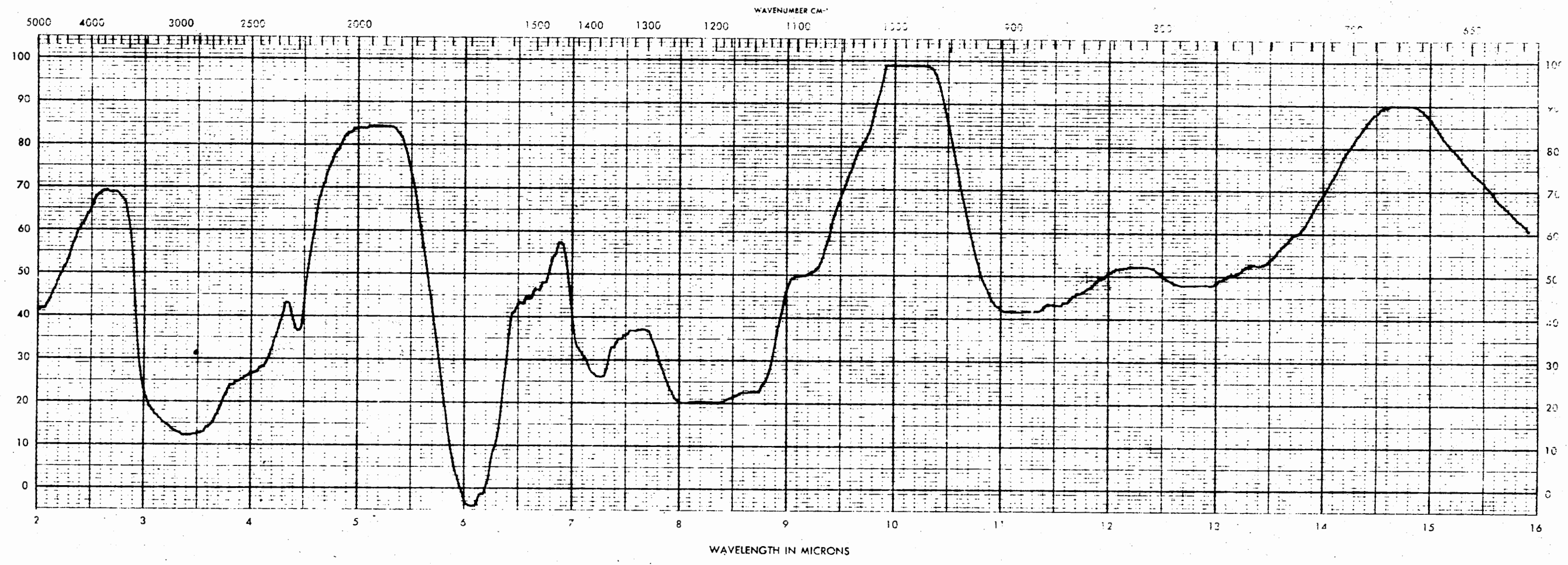


Figure 20. Infrared Spectrum of Isotactic Poly(acrylic acid)(X), KBr Pellet

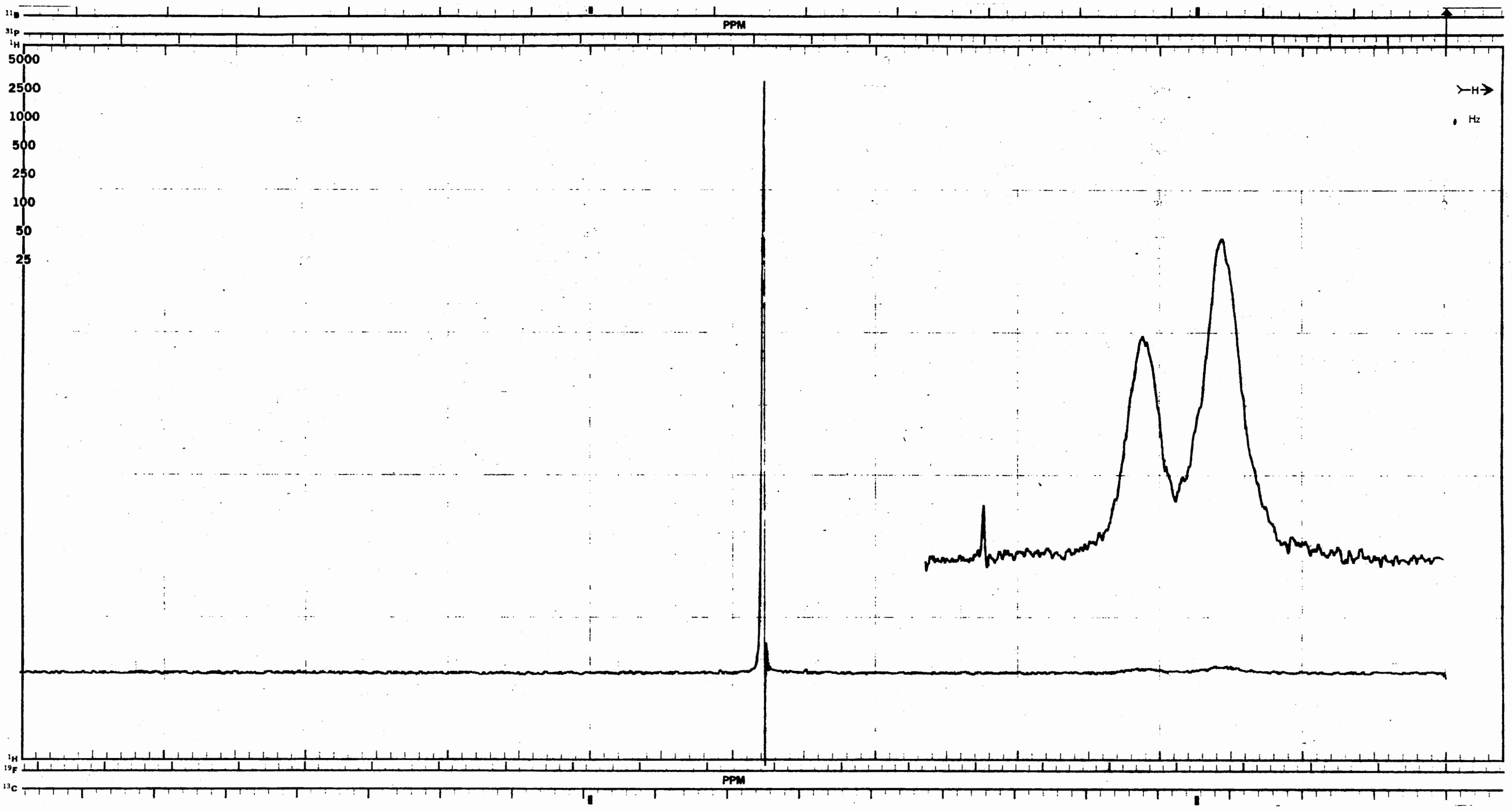


Figure 21. Proton Magnetic Resonance of Syndiotactic Poly(acrylic acid)(XI) - 100 MHz

R. F. 57 dB	S. W. 1000 Hz	S. A. 1.6
F. B. 2 Hz	S. T. 250 Sec	S. O. 83116 Hz

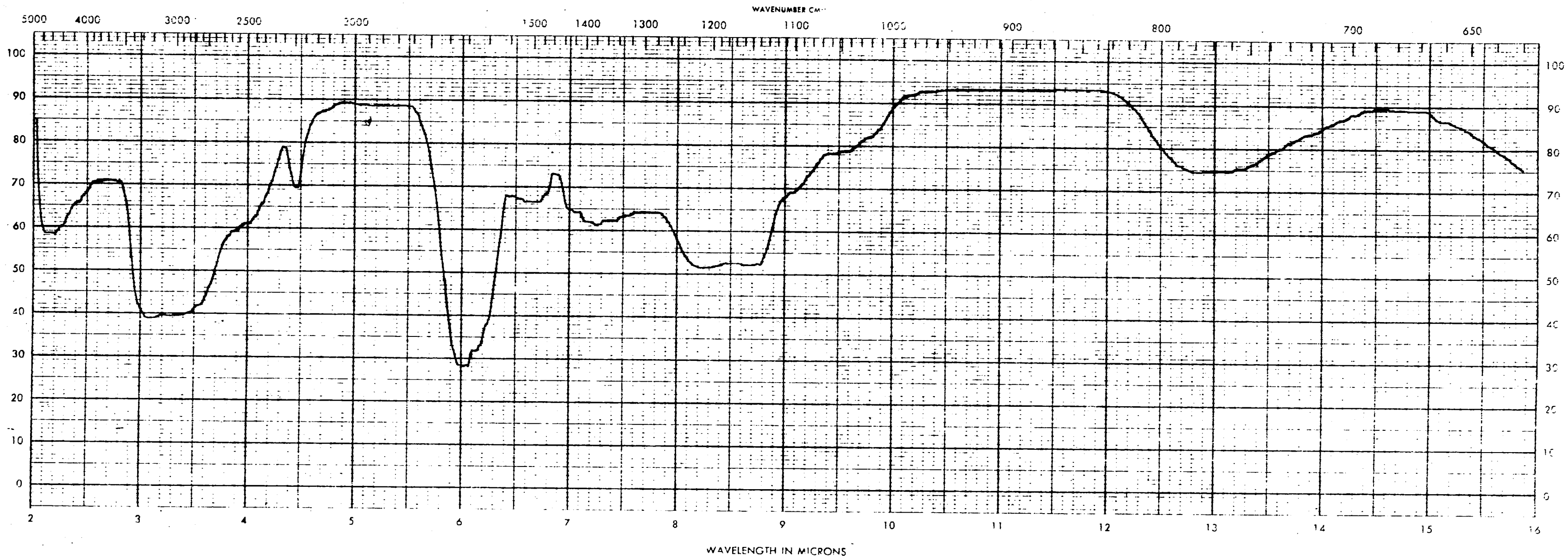


Figure 22. Infrared Spectrum of Syndiotactic Poly(acrylic acid)(XI), KBr Pellet

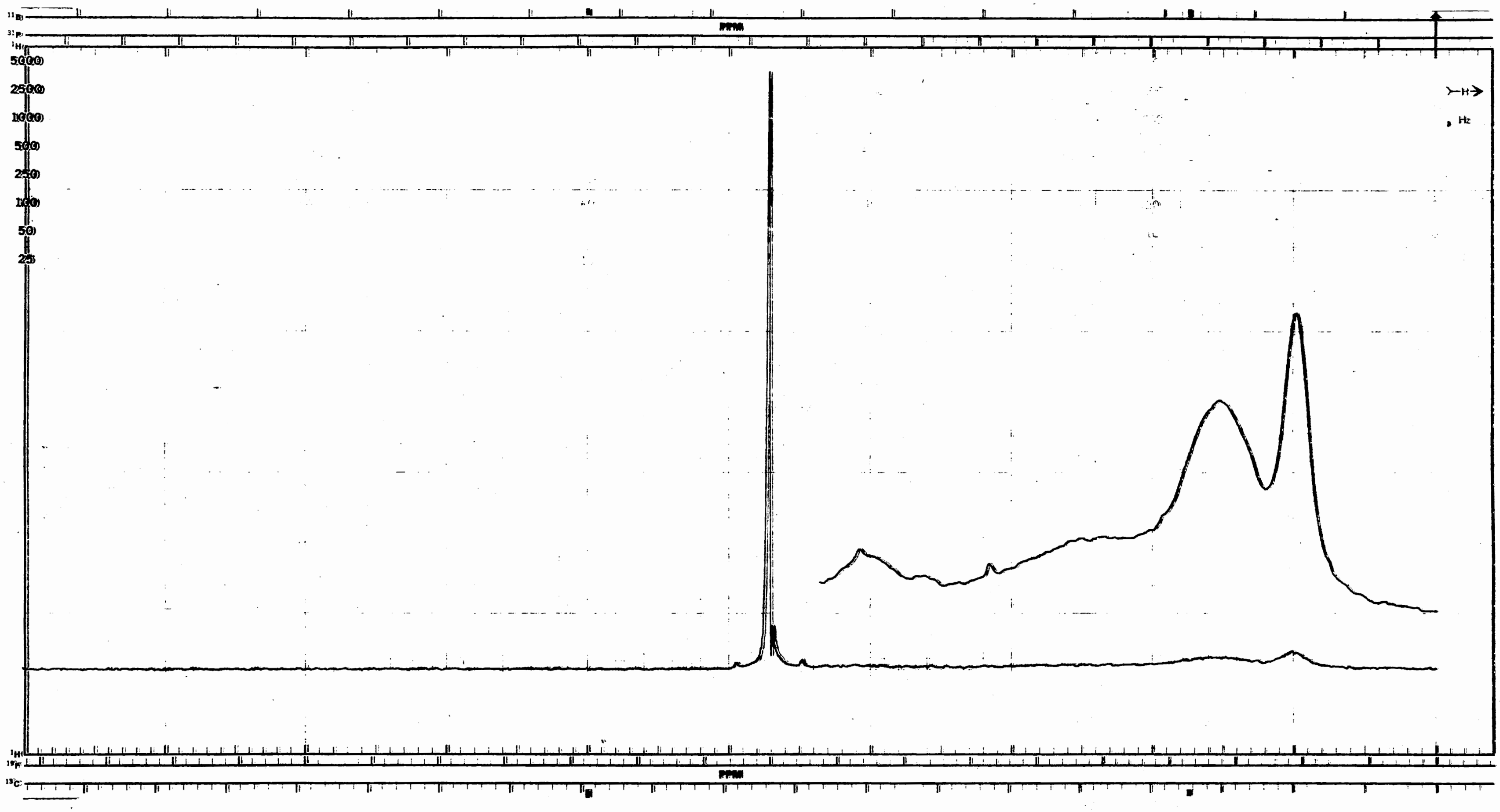


Figure 23. Proton Magnetic Resonance of Poly(itaconic acid)(XII) - 100 MHz

R. F. 65 dB
S. W. 1000 Hz
S. A. 1.25
F. B. 2 Hz
S. T. 250 sec
S. O. 83447 Hz

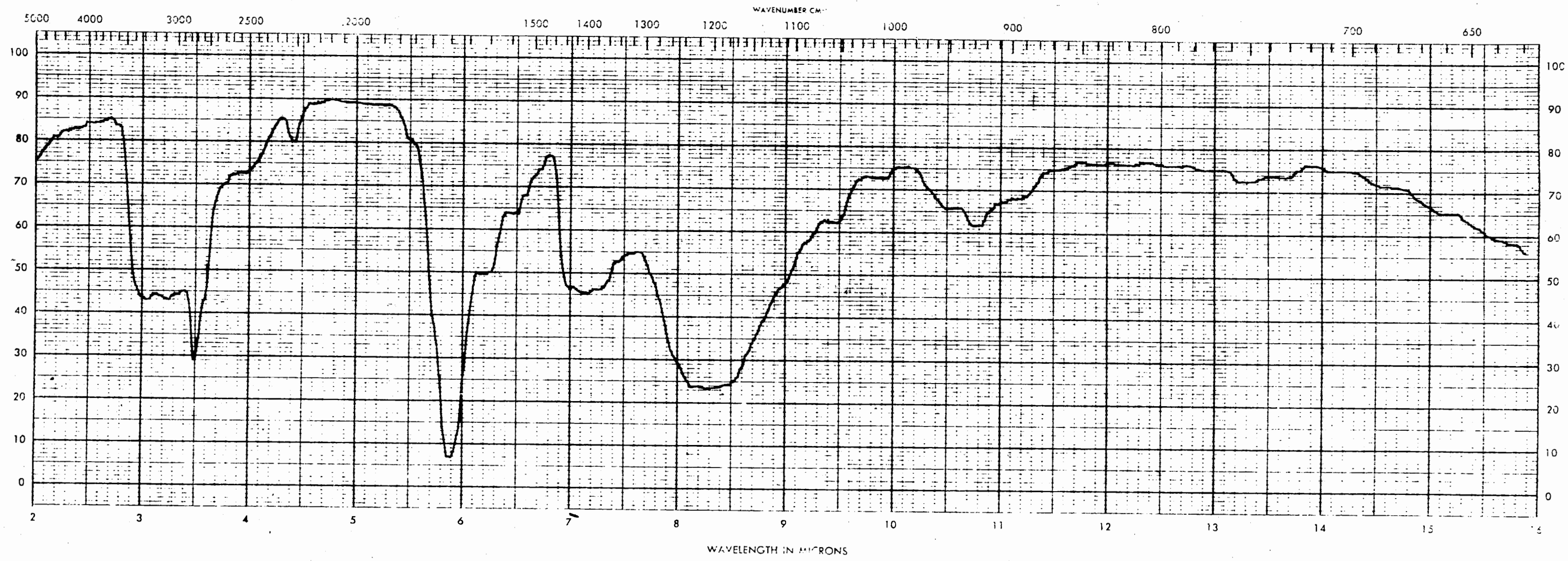


Figure 24. Infrared Spectrum of Poly(itaconic acid)(XII), KBr Pellet

$$\text{R-COOH} \rightleftharpoons \text{RCOO}^- + \text{H}^+ \tag{4}$$

Its thermodynamic dissociation constant, K_a, is expressed by

$$K_a = \frac{(\text{R-COO}^-)(\text{H}^+)}{(\text{R-COOH})} \tag{5}$$

where the parentheses denote the activity of each species. Often, however, the conventional dissociation constant, K_o, defined by

$$K_o = \frac{[\text{R-COO}^-][\text{H}^+]}{[\text{R-COOH}]} \tag{6}$$

is used instead of K_a since we do not know the activities of R-COO$^-$ and R-COOH but only their analytical concentrations (in brackets).

Equation 6 can be re-written as

$$\text{pH} = \text{p}K_o - \log[(1-\alpha)/\alpha] \tag{7}$$

where the degree of ionization, α, is defined by

$$\alpha = \frac{[\text{R-COO}^-]}{[\text{R-COO}^-] + [\text{R-COOH}]} \tag{8}$$

$\text{p}K_o$ may be related to the standard free energy change of the dissociation process, ΔG^o, as

$$\text{p}K_o = -\log K_o = -0.434\ \Delta G^o/RT \tag{9}$$

In the dissociation of polyelectrolytes, however, an additional amount of work, ΔG_1^o is required, thus Equation 7 may be modified to

$$\text{pH} = \text{p}K_o - \log[(1-\alpha)/\alpha] + 0.434\ \Delta G_1^o/RT \tag{10}$$

Here, ΔG_1^o can be expressed as

$$\Delta G_1^o = e\psi_b \tag{11}$$

in terms of the electrostatic potential at the place where H$^+$ originally existed, ψ_b • ΔG_1^o can also be expressed by

$$\Delta G_o^1 = dG_1^o/d\nu \tag{12}$$

where ΔG_1^o is the electrostatic free energy of the polyion having ν ionized groups.

It appears from published experimental evidence that the properties of poly(methacrylic acid) in aqueous solutions are somewhat peculiar. From their viscosimetric investigation on poly(methacrylic acid), Katchalsky and Eisenberg (62) concluded that the undissociated acid must be a highly coiled molecule, impermeable to the flow of the solvent. On ionization of the carboxylic acid groups the molecule unfolds, to assume a highly extended conformation.

During the first part of the titration (64) of poly(methacrylic acid), the electrostatic repulsion exerted on the chain segments of the molecule are counteracted by contractive forces, resulting on one hand from the conformational free enthalpy of the chain and on the other hand form the intramolecular attractive forces (e.g., hydrogen bonds and Van der Waals interaction). It is interesting to note that for poly(acrylic acid) the intramolecular interaction does not seem to play a similar important role in potentiometric and viscosity behavior.

This indicates that in the region where poly(methacrylic acid) changes from a dense coil to an expanded molecule the Van der Waals forces due to the methyl groups are important. This region may be interpreted as an interval where a conformational transition between two different molecular forms of poly(methacrylic acid) occurs.

The titration curves were all made by plotting pH vs. α (degree of ionization). The α was calculated as the ratio of titrant added at a specific pH to that required for complete neutralization. The plots of pH vs. $\log[(1-\alpha)/\alpha]$ are shown in Figures 26 and 28. Figures 23 and 27 show titration curves of polymers VIII, IX, X, XI and XII, for which the polymers were dissolved in excess standard sodium hydroxide and titrated with standard hydrochloric acid.

$$pH = pK_o - \log[(1-\alpha)/\alpha]$$

The parameters in the above equation for the above polymers are summarized in Tables XIX, XX, XXI, XXII and XXIII.

TABLE XIX

HENDERSON-HASSELBALCH PARAMETERS FOR TITRATION OF POLYMER IX

pH	α	$\log[(1-\alpha)/\alpha]$
11.56	1.00	-
11.26	0.89	-0.92
10.32	0.80	-0.60
9.86	0.74	-0.46
8.86	0.69	-
8.60	0.59	-0.16
7.29	0.49	-
6.84	0.39	-
6.56	0.34	0.29
6.00	0.28	0.41

TABLE XX

HENDERSON-HASSELBALCH PARAMETERS FOR TITRATION OF POLYMER VIII

pH	α	$\log[(1-\alpha)/\alpha]$
11.24	1.00	-
10.84	0.94	-
10.34	0.89	-0.92
9.30	0.84	-0.72
8.22	0.80	-
8.10	0.74	-0.46
7.5	0.69	-0.35
7.04	0.59	-
6.10	0.49	0.02
5.4	0.39	0.19
4.6	0.28	0.41

TABLE XXI

HENDERSON-HASSELBALCH PARAMETERS FOR TITRATION OF POLYMER X

pH	α	$\log[(1-\alpha)/\alpha]$
10.90	1.00	-
10.45	0.90	-0.96
9.7	0.84	-0.72
8.71	0.80	-
8.30	0.69	-0.35
7.5	0.59	-0.16
7.0	0.49	0.02
6.4	0.39	0.19
5.7	0.28	0.41
4.2	0.09	-

TABLE XXII

HENDERSON-HASSELBALCH PARAMETERS FOR TITRATION OF POLYMER XI

pH	α	$\log[(1-\alpha)/\alpha]$
10.4	1.00	-
10.01	0.94	-
8.46	0.89	-0.92
7.08	0.80	-0.60
6.38	0.69	-0.35
5.75	0.59	-0.16
5.1	0.49	0.02
3.5	0.28	-

TABLE XXIII

HENDERSON-HASSELBALCH PARAMETERS FOR TITRATION OF POLYMER XII

pH	α	$\log[(1-\alpha)/\alpha]$
12.3	1.00	-
11.70	0.89	-0.92
9.9	0.69	-0.35
8.8	0.49	0.02
8.1	0.39	0.19
7.5	0.28	0.41
6.8	0.19	0.63

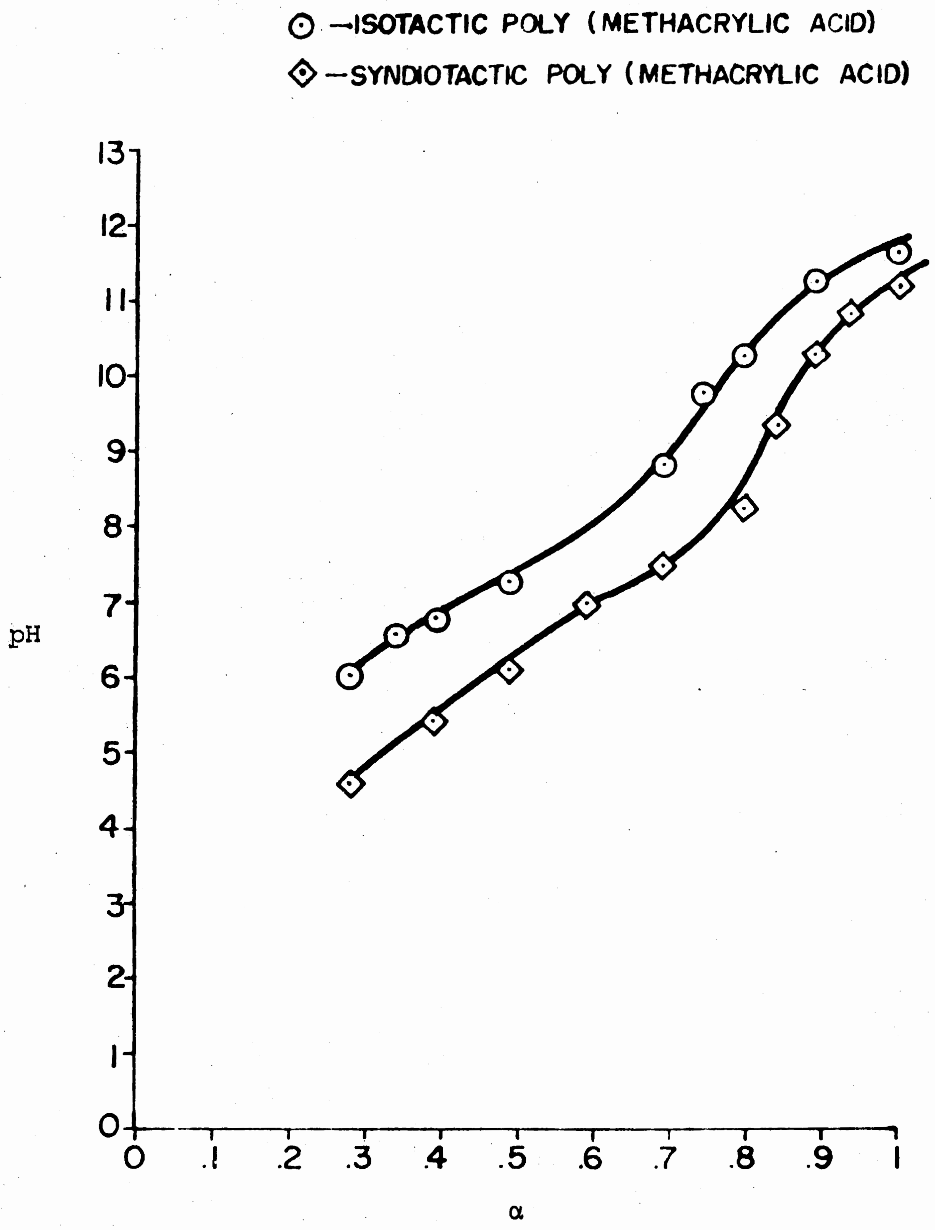


Figure 25. pH vs. α for Polymers IX (⊙) and VIII (⊡)

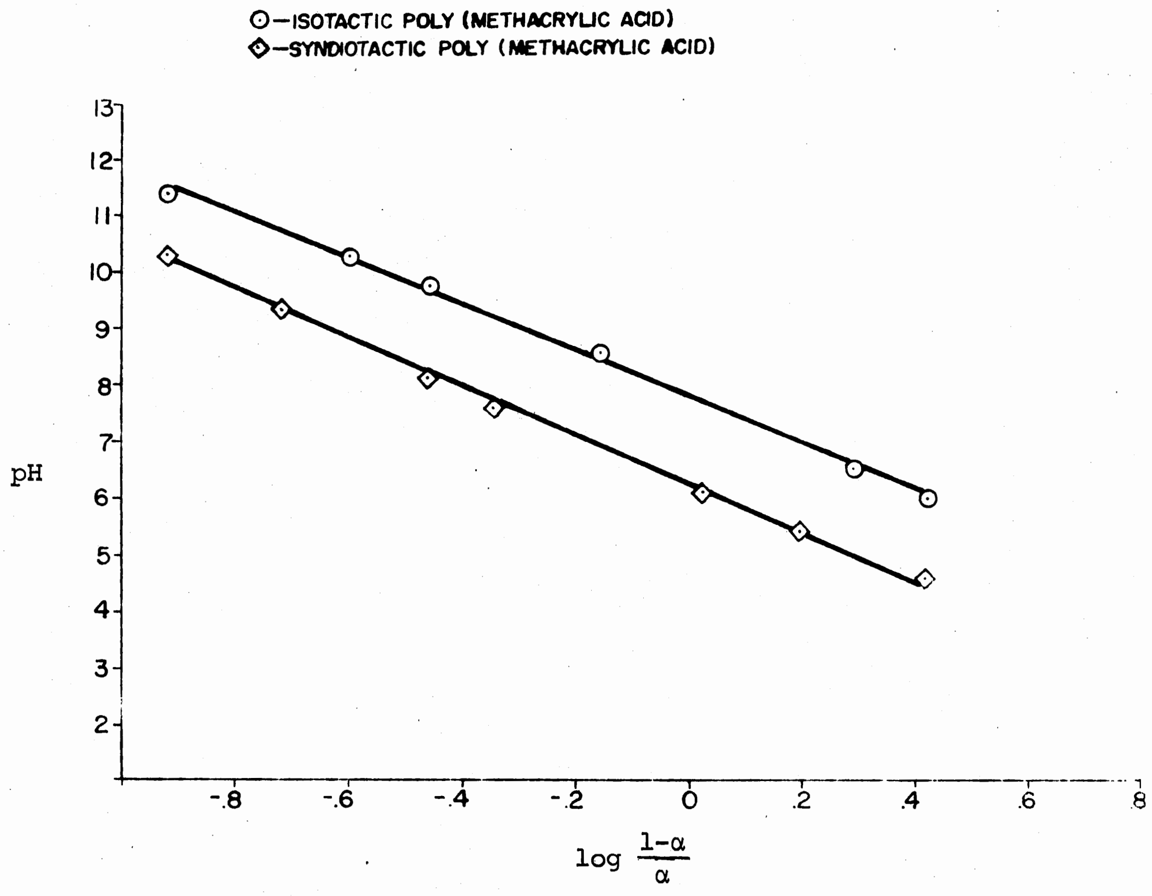


Figure 26. pH vs. log[(1-α)/α] for Polymers IX (⊙) and VIII (⊡)

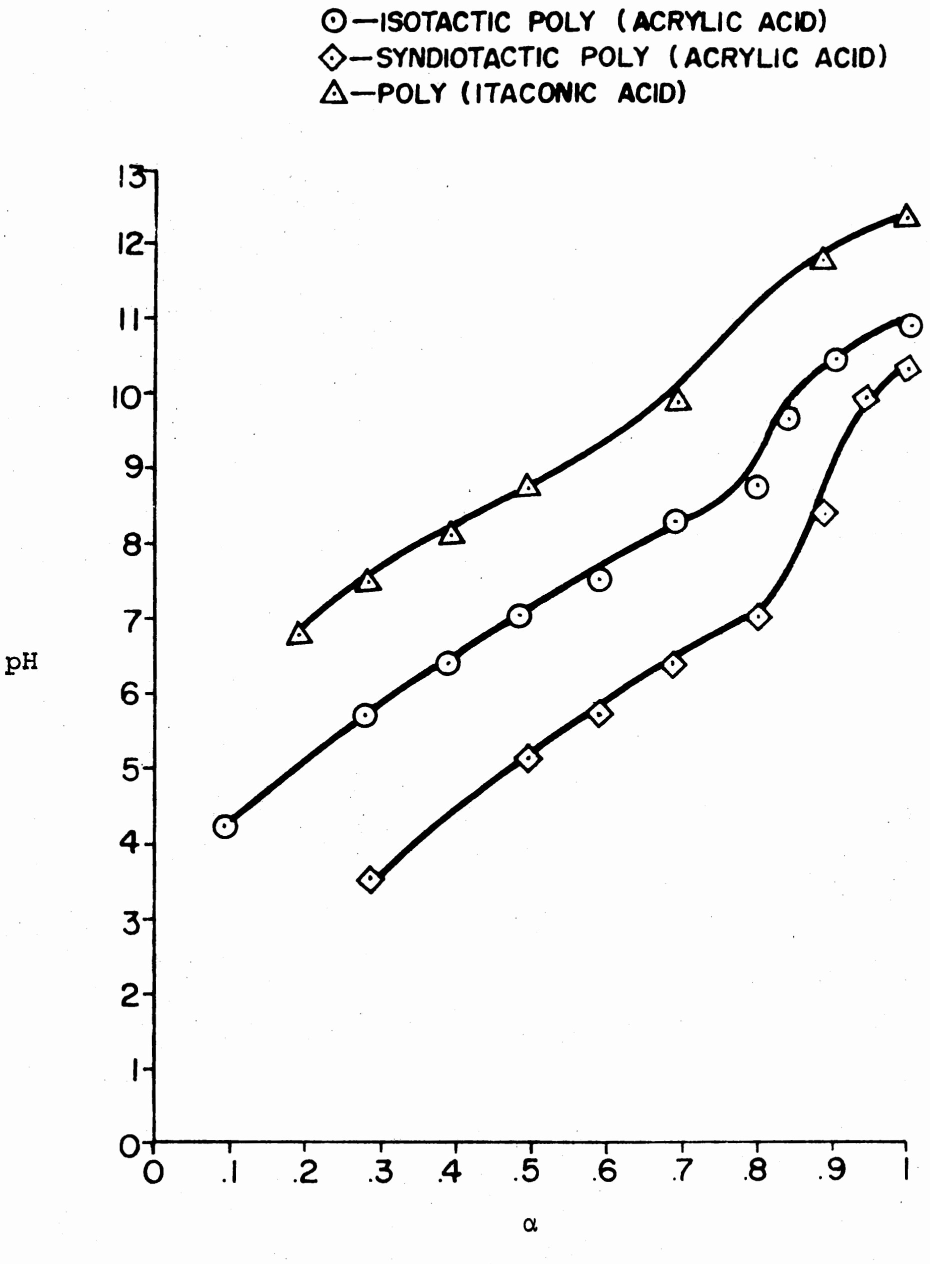


Figure 27. pH vs. α for Polymers X (⊙), XI (◇), and XII (△)

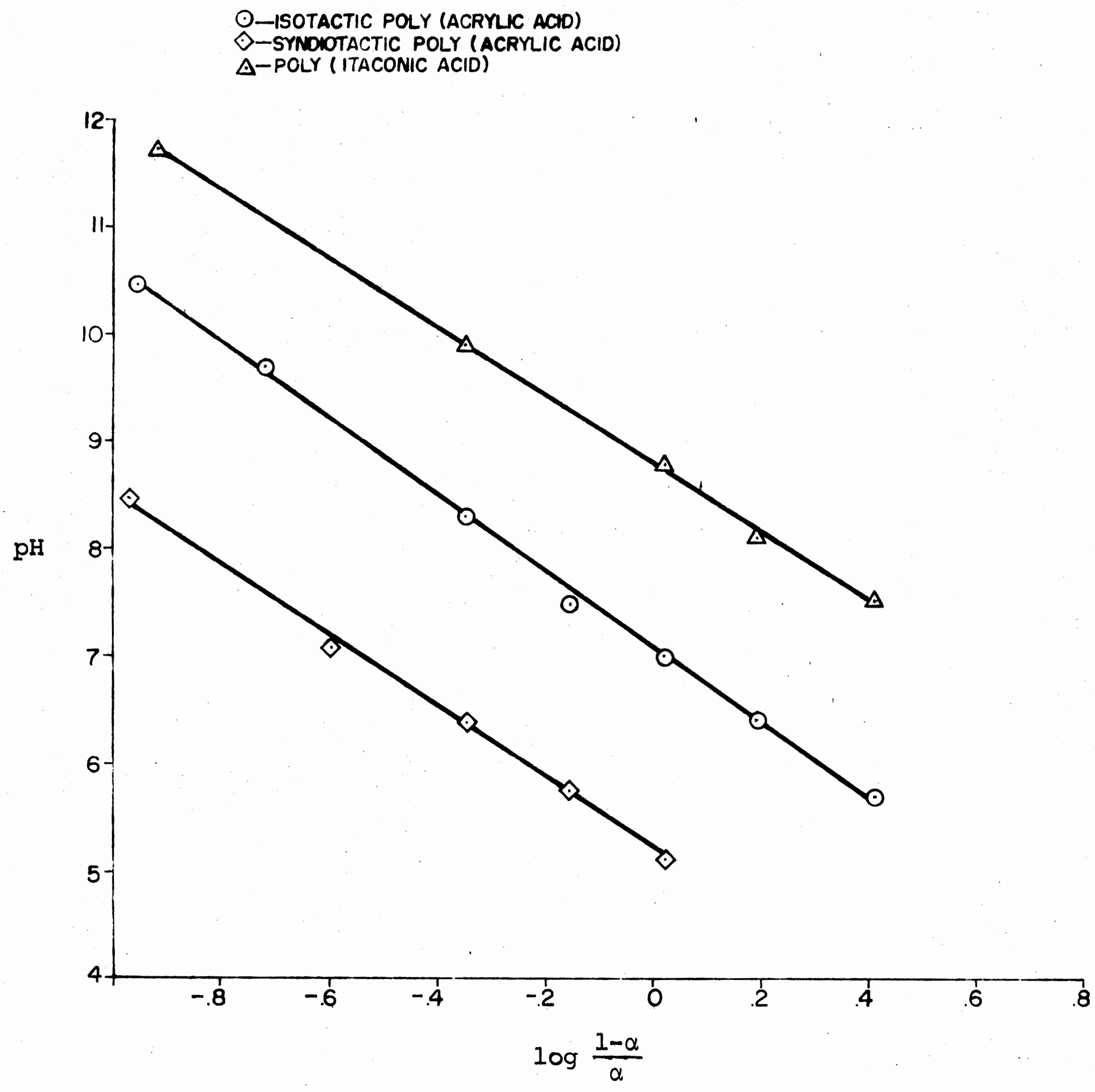


Figure 28. pH vs. log[(1-α)/α] for Polymers X (◉), XI (⊡), and XII (▲)

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