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Drug release of polymeric pharmaceuticals/

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DRUG RELEASE OF POLYMERIC PHARMACEUTICALS

A Dissertation Presented

By

WALTER DEITS

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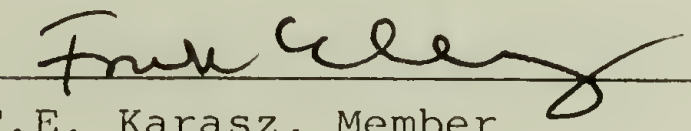
Approved as to style and content by:

Otto Vogl, Chairman of Committee



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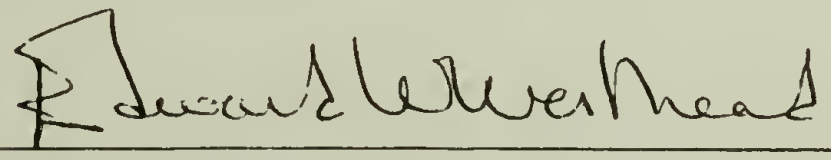

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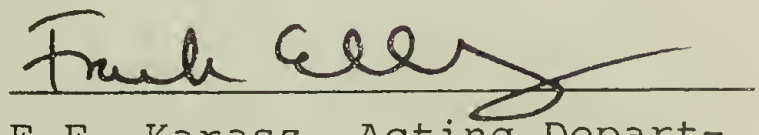

F.E. Karasz, Acting Department Head
Polymer Science & Engineering

For my mother

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ABSTRACT

Drug Release of Polymeric Pharmaceuticals

(September 1979)

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Directed by: Professor Otto Vogl

Several novel polymers containing selected monomers with known pharmaceutical activity as integral parts of the chain backbones were synthesized, and their hydrolytic stabilities examined, with the objective of determining the factors affecting the rate of release of the active agents from the polymer systems under conditions resembling those encountered in a physiological environment.

Primaquine(8-(4-amino-1-methylbutylamino)-6-methoxy-quinoline) was found to be difficult to incorporate into the backbone of a polymer chain. This was shown to be due to an unequal reactivity between the primary aliphatic and the hindered secondary aromatic amino groups. Side reactions associated with the quinoline moiety were also shown to be a source of problems. Primaquine was incorporated into several polymers of moderate molecular weight by forming biuret linkages with the primary amino group from a reaction between the drug and a diisocyanate.

Bithionol (2,2'-thiobis(4,6-dichlorophenol)) was synthesized in 43% yield from 2,4-dichlorophenol and sulfur dichloride. A variety of bithionol polyesters, as well as poly(bithionol phenylphosphate), poly(bithionol phenylphosphonate), and poly(bithionol phenylphosphinate) were prepared from bithionol and various diacid chlorides, phenyldichlorophosphate, phenyl phosphonicdichloride, and dichlorophenylphosphine, respectively. Reaction of bithionol with phosgene afforded a 40% yield of bithionol bischloroformate which was used to prepare a number of polycarbonates and polyurethanes from diols and diamines, respectively.

The hydrolytic stability of selected polymers was examined at 37°C and pH 7.4. Solubility was found to be the most important factor influencing the rate of hydrolysis. The polymers that were water soluble or at least water swellable were found to hydrolyze according to second-order kinetics and at a rate many times faster than polymers that were insoluble. The insoluble polymers were found to hydrolyze according to zero-order kinetics. The presence of hydrophilic polyoxyethylene segments was also found to enhance the rate of hydrolysis.

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INTRODUCTION

This dissertation describes the synthesis of selected polymers containing biologically active repeat units as well as the evaluation of these polymers as potential biodegradable sustained release agents. Although most of the discussions will concern biological applications, the concepts involved are by no means limited to biologically active polymers. The work described is part of an extensive effort in this laboratory in the general area of functional polymers and polymers containing functional groups. The discussions in this chapter are intended to complement much of this work.

Section I discusses the concept of polymeric pharmaceuticals in general and that of the sustained release of biological agents in particular. Sections II and III describe various methods of preparing polymers containing active pharmaceutical agents as well as some of the properties of these materials.

The general concept that polymers exhibit biological activity because they degrade or hydrolyze under physiological conditions is described in Sections IV and V.

The biological activities of the drugs used in

this study, namely primaquine and bithionol, are discussed in Section VI. This section is also intended to provide the background and justification for the evaluation and application of some of the materials produced during the course of this research.

Finally, in Section VII, polymers prepared from hindered bisphenols are discussed. This discussion is intended to provide insight into the polymerization behavior of some of the materials used in this work.

I. Polymeric Pharmaceuticals and the Sustained Release of Biological Agents--General Background

Pharmacologically active polymers and polymers containing repeat units that are pharmacologically active in their monomeric form have been attracting a great deal of attention in recent years, as evidenced by the number of recent publications and symposia relating to polymeric drugs.[1-15] Research in this area has had several objectives. For instance, by combining drugs with polymers, drugs otherwise unable to diffuse across cell membranes can be "carried" into the cell along with the polymer molecule.[16] The use of liposomes and of DNA-complexes as carrier agents for drugs has been shown.[17,18] Also, because of the expected localization of polymers within the body, high concentrations of drugs in certain areas can be expected with some polymer-drug systems. In addition, the

ease with which one can vary the structure and thus the properties of polymer systems (e.g., through copolymerization, crosslinking, etc.) should enable a number of different polymeric drugs with a variety of activities and cell distribution patterns to be synthesized. This is in contrast to low molecular weight drugs which often tend to lose their activity completely with relatively minor changes in structure.

The majority of work in the area of polymer drug systems, however, has concentrated on the sustained delivery of drugs at optimal rates and on the release of herbicides and insecticides with minimal effects on the environment. The need for a good controlled release technology is evident when one examines the present method of administering active agents. In both the medical and agricultural field active agents or drugs are conventionally dispensed at periodic intervals. This is necessary in order to maintain the concentration of active agent in the body or in the environment above a minimum effective level. Periodic applications of this sort have the drawback of yielding alternating high and low levels of the applied agent in the system. These periodic high concentrations of active agent can lead to undesirable side effects. On the other hand, the low concentrations may not be at a level sufficient to provoke the desired response in the system. This concept is illustrated in Figure 1. Smaller and more frequent doses

to minimize this problem are inconvenient and can lead to a large waste of material either because of deterioration or loss to the system. Clearly a system that released the active agent at a constant and controllable rate over a long period of time would result in less wastage and fewer side effects than conventional methods of drug administration.

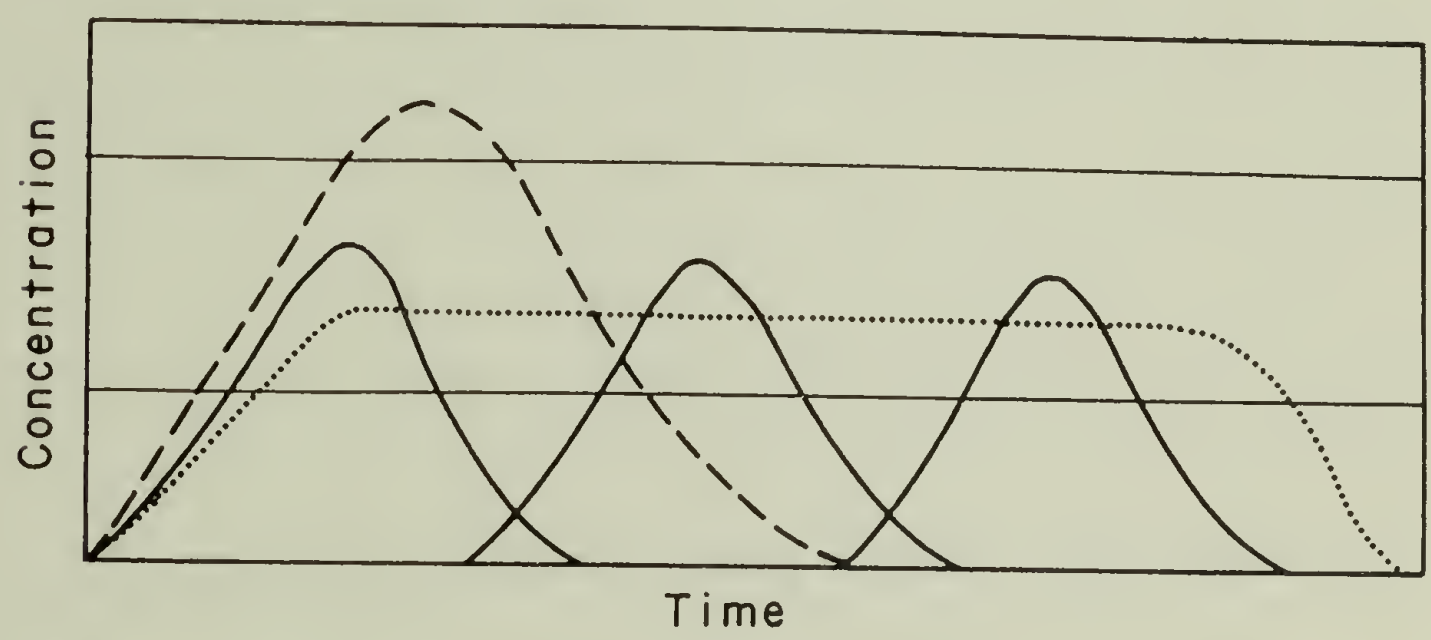


Figure 1. Schematic illustration of drug concentration time profile after administration.

———— standard dose
- - - - overdose
····· ideal dose

II. Preparation and Properties of Polymeric Pharmaceuticals and Sustained Release Formulations

A number of different methods of controlling the rate of release of active agents have emerged over the past few years, nearly all of them incorporating polymers as a

part of the controlled release mechanism. The various techniques of controlling the release of active agents can generally be classified into a few basic categories:

A. Membrane encapsulated reservoir devices. In this technique the active agent is completely surrounded by a polymeric membrane. It is this membrane that controls the rate of release of the active agent. Ideally, the agent should be dispersed as a homogeneous suspension or solution within the membrane in order to maintain a constant activity of the agent in the reservoir, as is shown in Figure 2.

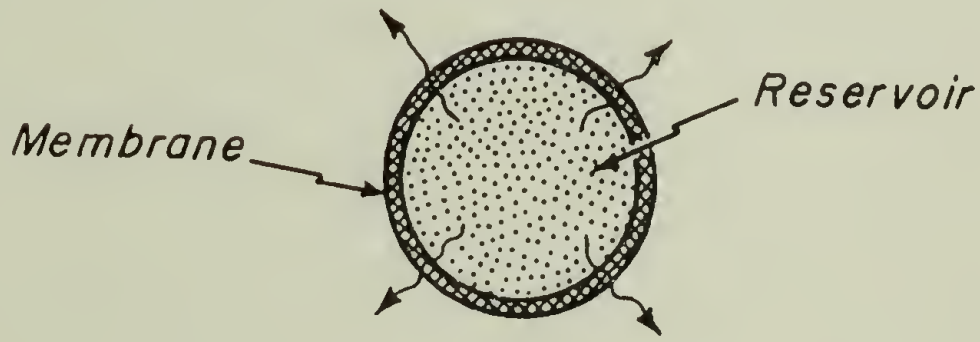


Figure 2. Membrane encapsulated reservoir device.

The release rate should decay more or less exponentially with time as the agents activity in the reservoir decreases as expected for first order kinetics. These membrane devices may be nearly any size, i.e., from microencapsulation to macroencapsulation.

B. Matrix devices. Matrix devices are systems where the active agent is not encapsulated per se as in I above, but rather is dispersed throughout a polymer carrier. In this type of system the agent migrates out of the device and into the environment, with a rate dependent on the rate of diffusion of the agent through the carrier or matrix, as shown in Figure 3. Here again, the rate is generally not zero order.

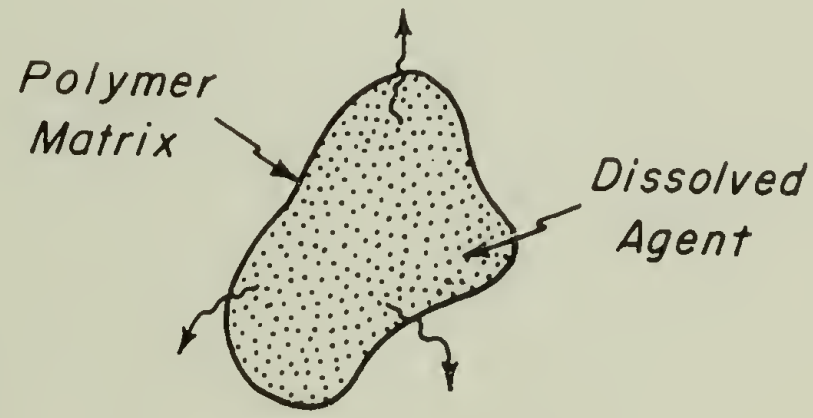


Figure 3. Matrix device.

In a matrix device the active agent may be able to diffuse through the matrix on its own at a reasonable rate, or it may require some environmental agent such as water to penetrate or swell the device in order to facilitate its diffusion. This environmental agent could act to physically unbind the active agent from the matrix, or it could act as a simple plasticizer enabling diffusion to occur at a faster rate.

C. Reservoir devices without a membrane. This category includes devices such as hollow fibers filled with the agent which is released through the open ends of the fiber rather than through the walls. Also included are porous networks, the pores of which contain the agent to be released.

D. Erodible devices. One of the most promising classes of devices for the controlled release of biologically active agents are erodible polymer carriers. These can be of several types. One type consists of polymeric backbones, either linear or crosslinked, with the active agents chemically attached to them as pendant groups (Figure 4a,b). As the linkages connecting the active agent to the polymeric carrier are eroded, e.g., hydrolyzed, by environmental agents, the active agents are released, leaving the polymer backbone behind. Another type consists of the incorporation of the active agent into the backbone of a polymer chain (Figure 4c). As the linkages holding the chain together are broken, the active agent is freed and enters the environment. In another, somewhat similar system, the active agent is dispersed throughout an erodible polymer matrix (Figure 4d). As environmental agents erode the polymer carrier, the active agents are released into the surroundings. In formulations of the latter two types the controlled release device itself actually disappears as

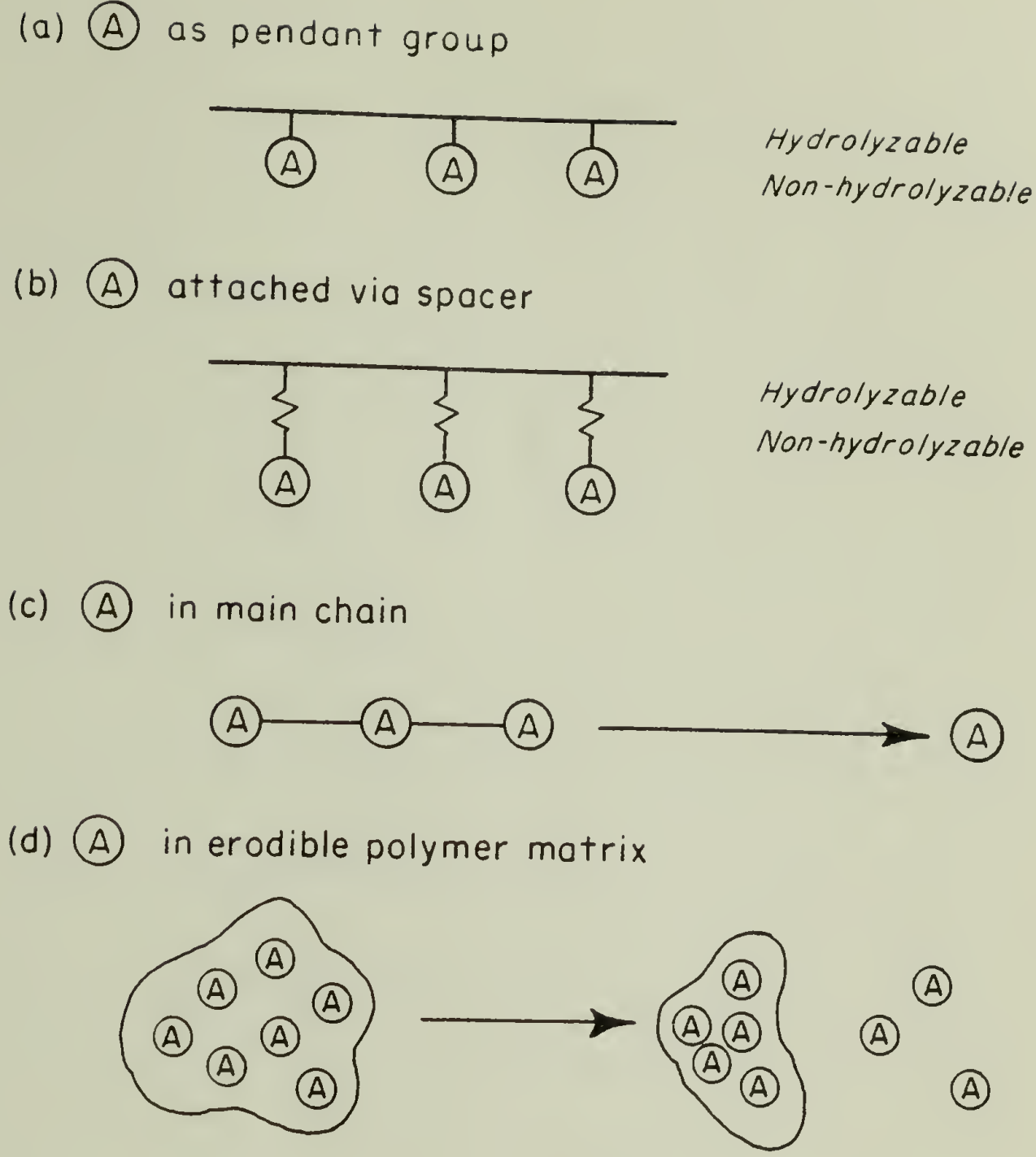


Figure 4. Erodible polymer carriers.

the active agent is released. This has the obvious advantage of no residual polymer carrier in the body or environment. The erosion products would of course have to pose no health or environmental hazards of their own.

All of the above mentioned systems have been investigated to some degree as potential controlled release

polymer systems with many examples cited in the literature.[10,11,19-24] A number of commercial products have already been introduced, a few of which are shown in Table 1.

As can be seen from the table, most of the devices on the market today employ a membrane or matrix device rather than erodible devices with the active agent actually bonded to the carrier. This is not due to any particular advantage inherent in these systems, but is instead due to the fact that this area is a relatively new field with much work to be done. The systems that were initially easier to formulate and test were generally examined first. A number of studies have been made, however, of methods that incorporate active agents into polymer systems as chemically bonded species.[6,11,12] These studies have brought out a number of advantages that chemically modified devices have over other types of polymeric formulations. These advantages include the prevention of premature release, or leaching out, of the active agent, an ability to design the chemical system to meet the requirements of the body or environment, and the disappearance of the polymer carrier.

In order to chemically combine compounds with polymers the required biologically active agent, or drug, may be complexed,[19,20] or bonded ionically[12,21-24] or covalently[6,12,13] with a variety of macromolecular substances. The

TABLE 1

SOME COMMERCIAL CONTROLLED RELEASE PRODUCTS[10]

Trade Name	Company	Comments
NOFOUL	B.F. Goodrich	Antifouling rubber coating. Matrix device (some versions employ a membrane in addition)
NO-PEST STRIP	Shell	A matrix device for release of insecticides
HERCON DISPENSER	Health-Chem	A laminated membrane device for release of pesticide and other agents
PRECISE	3M	Microencapsulated fertilizer
OSMOCOAT	Sierra	Microencapsulated fertilizer
PENNCAP-M	Pennwalt	Microencapsulated methyl parathion insecticide
OCCUSERT	Alza	Laminated membrane device for release of pilocarpine in the eye for glaucoma control
PROGESTASERT	Alza	A membrane reservoir device for release of progesterone in the uterus for birth control
BioMET SRM	M & T	A matrix device for release of a molluscicide
INCRACIDE E-51	International Copper Research Association	A matrix device for release of a molluscicide

use of each of these techniques has been extensively treated elsewhere,[6,13-15] consequently a complete review will not be presented here. A brief description of the methods involved, as well as a few examples of each, will be presented, however, in order to illustrate the concepts involved.

E. Chemical complexes. Many compounds form chemical complexes with a variety of polymeric systems. It has been shown that some polymers such as polyvinylpyrrolidone,[25-27] polyethylene glycol,[28] dextran,[29] polyethoxypolypropoxyethanol,[30] polyvinylalcohol,[31] and starch[32] form complexes with iodine that show antimicrobial activity. In a review of the field of iodine-polymer complexes,[33] Mokhnach showed that the presence of the cation $I(I^+)$ is responsible for the antimicrobial properties. The decrease in toxicity of iodine when complexed with polymers was also demonstrated.

A number of other complexes have been synthesized for their use as long-acting formulations. Included are complexes of polyvinylpyrrolidone with iodine monochloride and other halogen halides for use as antiseptics[34] and iron-dextran complexes for the treatment of anemia.[35]

F. Ionic polymers. Many polymers possessing ionic groups have been found to be physiologically active in their own right, as well as useful as carriers for a number of different drugs and pharmaceutical preparations. Sulfate esters

of partially hydrolyzed dextran,[36] glycogen,[37] starch,[38,39] and carboxymethylcellulose[40] have been shown to be effective blood anticoagulants. Dextran phosphates that increase the glucose content of the blood have also been synthesized.[41]

Polymeric ion-exchange resins have been attracting a great deal of interest as a means of prolonging the action of ordinary pharmaceutical preparations. The salt of a drug and an ion-exchange resin can be gradually decomposed in the gastrointestinal tract, enabling the liberated drug to exert its therapeutic action. A great number of these long-acting drugs have been patented in Great Britain, including salts of ion-exchange resins with vitamins[42] and salicylates.[43] Ion-exchange resins made from sulfonated benzene/divinylbenzene copolymers seem to be the most frequently used, but acrylic, methacrylic, and maleic anhydride containing resins have shown considerable promise.

Abrahams and Linnell[44] showed that the rate of release of a drug from an ion-exchange resin salt depends entirely on the presence of ions and is independent of the action of enzymes and other physiological factors. Since the total concentration of ions in the gastric juice changes within fairly narrow limits, the rate of release of drugs from ion-exchange resins remains reasonably constant. This constant release rate contrasts with the rate of release of drugs from tablets and capsules with special

coatings, since the decomposition of the coatings depends on a number of physiological factors.[44]

Although there is a considerable amount of literature on the use of ionic polymers as carriers for pharmaceutical preparations, there has yet to be completed a systematic study of pharmacological and clinical trials of these long-acting preparations.

G. Covalent compounds. Active pharmaceutical agents can be covalently bonded to polymers in one of three ways, as was shown earlier in Figure 4 (a-c). The incorporation of active agents into the backbone of a polymer chain (Figure 4c) will be discussed in Section III. The preparation of polymers with active agents covalently bound as side chains or pendant groups can be accomplished through either (i) polymerization of functional monomers, or (ii) reactions on polymers. These methods are illustrated in Figures 5 and 6. Both methods have been utilized to give different materials with properties useful for a variety of applications.

Covalently bonded drugs may act in one of two ways. First, the covalent bond between the drug and the polymer chain may slowly degrade, thus releasing the drug in its low molecular weight, pharmacologically active form. Second, the polymer-drug macromolecule may remain intact and exert its influence as the active polymer. Both of

Figure 5. Schematic illustration of the synthesis of functional polymers via the copolymerization of active monomer (A) with comonomer (C).

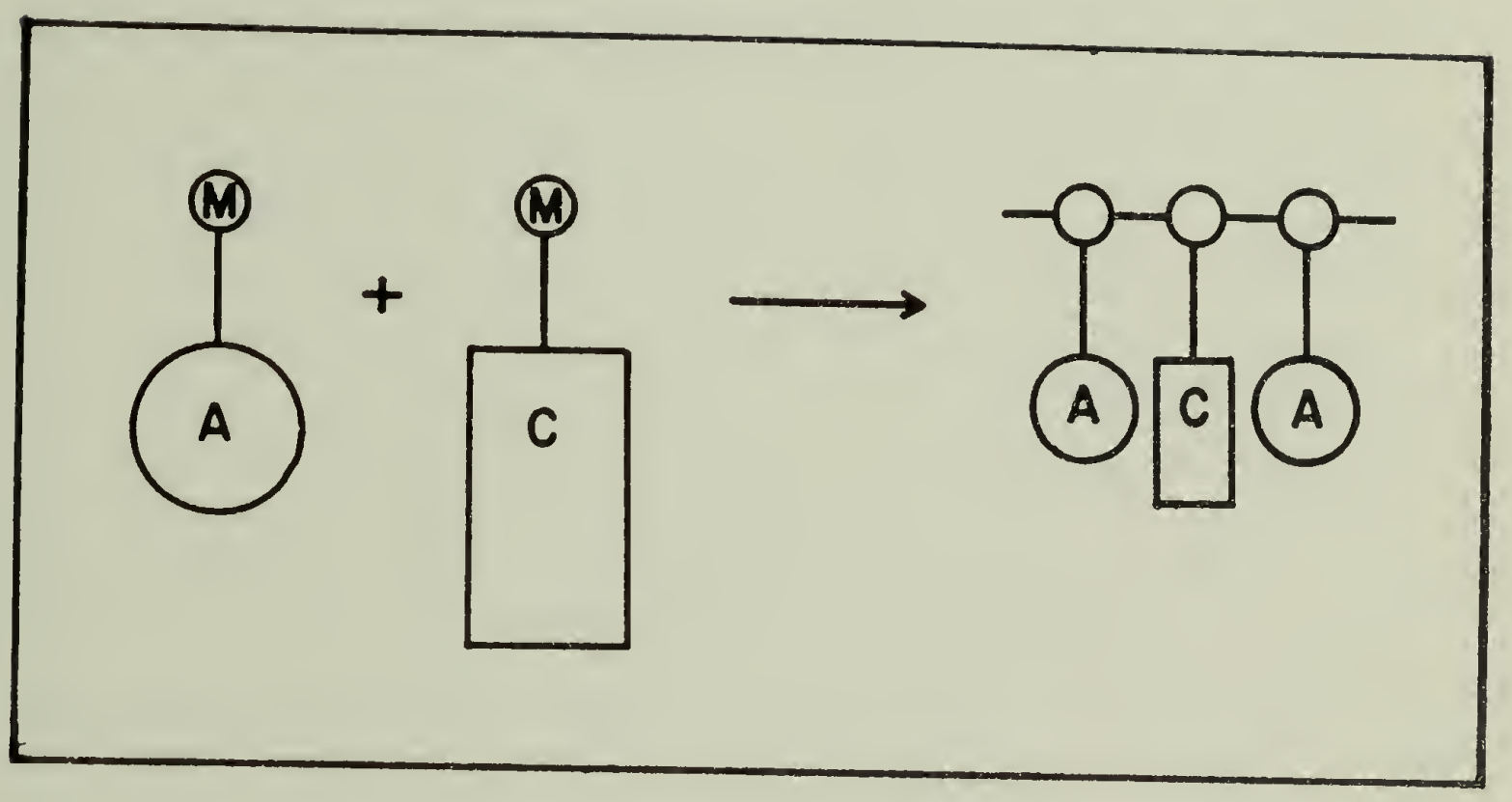
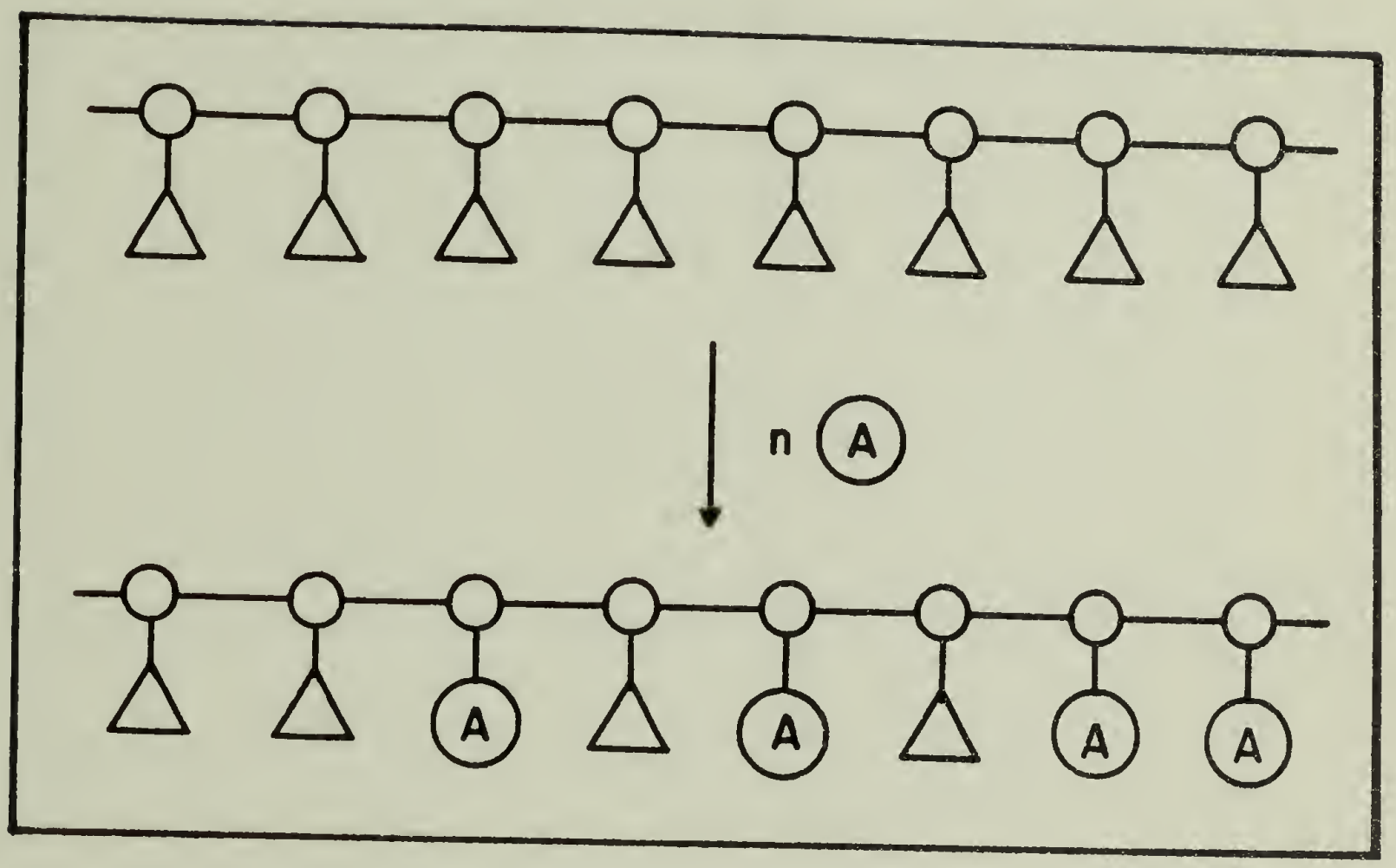

M
A
+
M
C
A
C
A

Figure 6. Schematic illustration of the synthesis of functional polymers via polymer reaction. (A) is the active functional group.


n
A
A
A
A
A

these means have been studied with very promising results. Bailey[45] synthesized a number of polymers with ultraviolet absorbing pendant groups. These included poly(methyl 5-vinylsalicylate) and poly(methyl 5-vinylacetylsalicylate). Further work by Tirrell[46] on the preparation of polymers and copolymers of 4- and 5-vinylsalicylate acid derivatives showed that the polymers not only exhibited substantial ultraviolet absorbing ability, but they also exhibited considerable antibacterial behavior. Although the salicylate moieties are attached to the polymer backbone via nonbiodegradable carbon-carbon bonds, considerable activity was observed in several of the polymers against both E. coli and B. subtilis. This activity did not seem to be due to the presence of trace amounts of residual or "extractable" monomer as the antibacterial activity of many of the polymers and copolymers were found to be selectively different than that exhibited by the monomers themselves.[46] In addition, poly(vinyl uracil) and poly(vinyl adenine), which are resistant to chemical and enzymatic hydrolysis,[47] have been shown to possess considerable antiviral activity, particularly at molecular weights greater than 100,000.[48]

Polymeric antifungal compounds have also been made by grafting the active antifungal agent pentachlorophenol onto ligno-cellulosic fibers.[49] Fungal attack on the system probably releases the pentachlorophenol from the

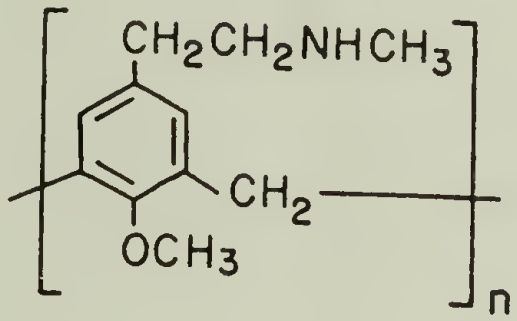
polymer backbone, thus providing the antifungal activity observed. Allan and coworkers synthesized a variety of polymeric herbicides by grafting active compounds such as phenoxyacetic acids onto various natural and synthetic polymer chains.[16] The slow release of the active herbicides provided protection for long periods of time with one application of a weight equivalent to that of a single dose of the low molecular weight compounds. The literature contains a number of additional examples of the controlled or sustained release of pharmacologically active compounds covalently bonded to polymers.[6,50-52]

III. Preparation and Properties of Polymeric Pharmaceuticals Incorporating Active Agents in the Main Chain

In addition to polymers carrying active pharmaceutical agents as pendant groups, polymeric drugs may also be obtained by incorporating active agents directly into the backbone of a polymer chain. These polymers are usually obtained through the direct condensation of drugs possessing multiple functionality. The prerequisite that at least two functional groups be present necessarily limits the number and type of drugs suitable for incorporation into polymer backbones. Despite this limitation, a number of drugs could be used for the synthesis of such polymers. Although relatively few polymeric pharmaceuticals of this type have been prepared, a number of advances

have been made, many of which show considerable promise.

As early as 1949 Baltzly[53] prepared a hypotensive agent of the type I by the condensation of formaldehyde with N-[2-(4-methoxyphenyl)ethyl]-N-methylamine. These



I

oligomers (n=3-4) showed very high and long-lasting activity. Utilizing the known ability of multiple quaternary ammonium groups to act as muscle relaxants, Schueler and Keasling[54] synthesized ionene polymers containing quaternary ammonium groups in the polymer chain. A number of the polymers showed a prolongation of activity with a factor greater than 10. Fernö and coworkers[55] also showed the same kind of activity prolongation with a polymer made from estradiol coupled with phosphate groups. The activity was shown to be due to the slow hydrolysis of the polymer chain since after radioactive marking free estradiol could be detected in the urine. Donaruma and coworkers have synthesized a number of sulfonamide-formaldehyde copolymers possessing antimalarial activity.[56-59] Polymers and copolymers of 4,4'-diaminodiphenylsulfone were

also prepared and tested.[59,60] In some cases the polymer tested had greater antimalarial activity and was less toxic than the corresponding monomeric sulfanilamides and sulfones. Their studies also showed that the antimalarial activity of the copolymers was not solely dependent on the sulfanilamide used, but also depended on the comonomer incorporated into the polymer chain.[58] A piperazine-carbon disulfide copolymer has been prepared by Dunderdale and Watkins[61] as a long-lasting anthelmintic that in an acid medium may slowly degrade to monomer or oligomer giving sustained anthelmintic effects from the two active monomers. It should also be mentioned that although antibiotics of long-lasting activity are of very great interest, the preparation of polymeric derivatives of penicillin has met with only limited success.[62] Polymers have been made through the opening of the lactam ring, however, these showed very little activity against microbes, undoubtedly due to the fact that the lactam ring is essential for antibiotic activity.[63]

During the condensation of these multifunctional agents, two or more functional groups are generally chemically altered, or substituted, therefore causing a probable loss of activity. This is not completely undesirable, however, as the biological activity may be regenerated in the organism by the cleavage of the linkages connecting the active agents to one another. This degradation of the

polymer chains should then release the original drugs into the organism in their active low molecular weight form. The rate at which these polymeric drugs degrade, and hence the time of action or activity of the polymers, is dependent on a number of factors, all of which are difficult to predict. Due to the fact that these polymers possess new physical, biological, and pharmacological properties, the results of many of the studies performed to date are difficult to assess and are at times even contradictory.

When designing a polymeric pharmaceutical system, one must take these various factors into consideration. For instance, when polymeric drugs are introduced into the body or environment they must degrade or break down into smaller biologically active segments if the original polymer drug system itself is not active in its own right. In order to do this, links in the macromolecular structure must be present that, when in a physiological environment, will degrade with time. One of the major routes of degradation is hydrolysis.[64] For this to occur at a significant rate, not only must hydrolyzable linkages such as esters, urethanes, or amides be present, but they must be accessible to those agents controlling hydrolysis. In bulk form only those polymers that are sufficiently hydrophilic will hydrolyze to any great extent. These include some polyamides, polyurethanes, and the polyesters of phosphonic, phosphorous, and phosphoric acids. In contrast

to these, some polyesters such as polyethylene terephthalate are quite stable to hydrolysis due to their hydrophobicity which excludes water from all the ester linkages except those on the surface, where degradation proceeds slowly.

In solution, or in a highly swollen state, on the other hand, all the linkages present in a polymer chain should be relatively accessible by water and other low molecular weight compounds. In this state the degradation of hydrolyzable polymers should be much faster than in the more closely packed bulk state, as the rate of hydrolysis is essentially controlled by the accessibility of the hydrolyzable linkages. Therefore, by varying the physical state of the polymer itself, as well as the nature of the linkage connecting a drug to or into a polymer chain and thus its resultant hydrophilicity or hydrophobicity, a variety of rates of hydrolysis in physiological environments should be able to be observed. Hydrophilic groups introduced into the polymer chain could also help solubilize or swell systems that are otherwise insoluble or non-swellable by physiological agents.

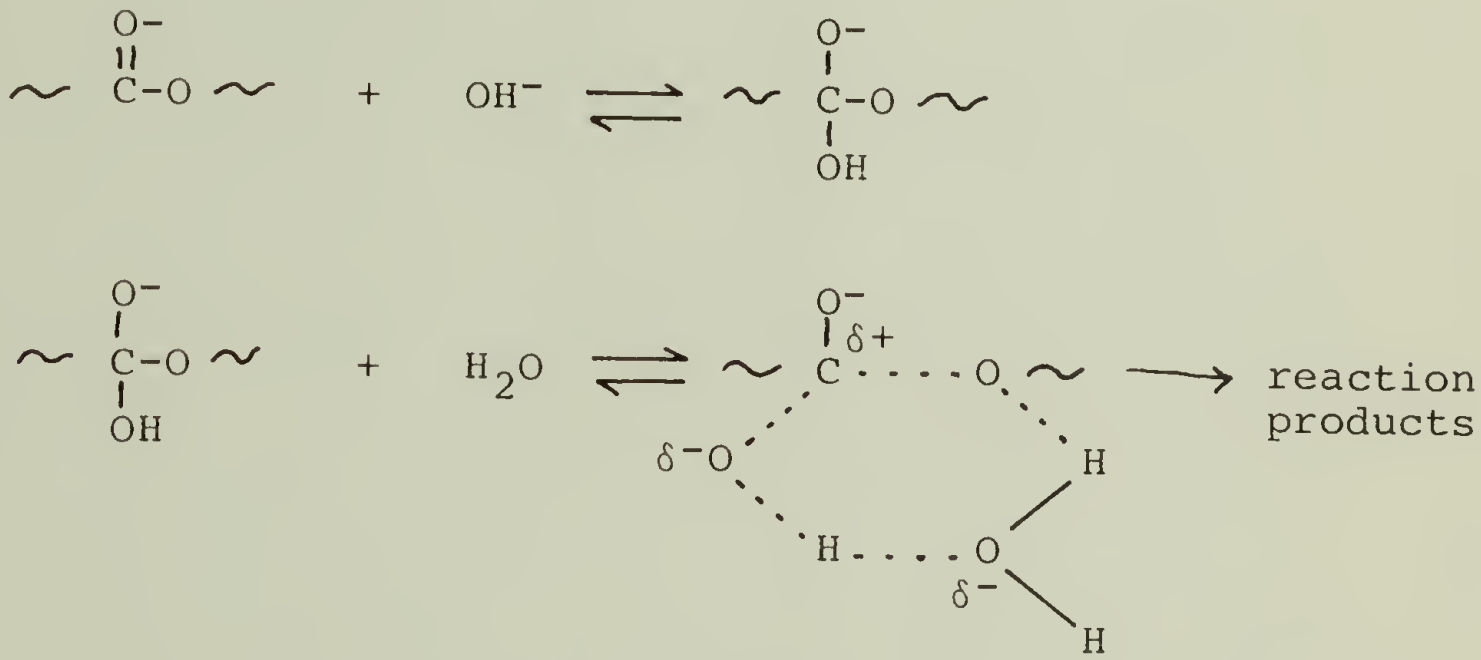
In order to put these concepts to use, drugs can be polymerized, copolymerized, or grafted onto already existing polymers using various connecting units with different hydrolytic stabilities. A study of the relative rates of hydrolysis, subsequent drug release, and the

physiological effects of these would be a valuable addition to the field. A fundamental study of this type as it applies to controlled release polymeric formulations has not been made at the present time, however some studies concerning the rate of hydrolysis of certain side chain moieties have been carried out by Morawetz and coworkers,[65-68] as well as others.[12] A complete investigation of the factors affecting the hydrolysis of the backbone of a polymer chain as they apply to polymeric drug delivery systems is still needed. Most of the studies to date have only involved single polymer-drug systems and their suitability for particular biological uses. A basic study of the type outlined above is needed in this area to bring together the many variables inherent in erodible polymeric drug systems.

IV. Hydrolytic Degradation of Synthetic Polymers

Although there is a vast amount of literature concerning the kinetics and mechanisms of hydrolysis of monoesters, relatively little fundamental work on the hydrolysis of polyesters has been done. In 1950 Waters[68] examined the alkaline hydrolysis of polyethylene terephthalate (PET), however, he did so at only one alkali concentration. Rudakova and coworkers,[69] on the other hand, studied the kinetics and mechanism of hydrolysis of PET films at

temperatures of 27 to 93°C and at KOH concentrations of 8.2-39.15%. They found that the hydrolysis of PET took place only at the surface and the reaction is of zero order for the polymer. It was also shown that the hydrolysis took place by a mechanism in which the rate-limiting step was the attack of the water molecule on the ionized form of the ester bond. They represented the mechanism as follows:



This is equivalent to the bimolecular basic hydrolysis mechanism with acyl-oxygen fission ($B_{Ac}2$) of Day and Ingold[70] for the hydrolysis of monoesters. Several other workers have examined the hydrolysis of polyesters under alkaline conditions arriving at essentially the same conclusions.[71]

The acid hydrolysis of polyesters catalyzed with hydrochloric acid and p-toluenesulfonic[72] acid gave hydrolysis rates for polyesters of aliphatic diacids 280 times faster than polyesters of aromatic diacids. The

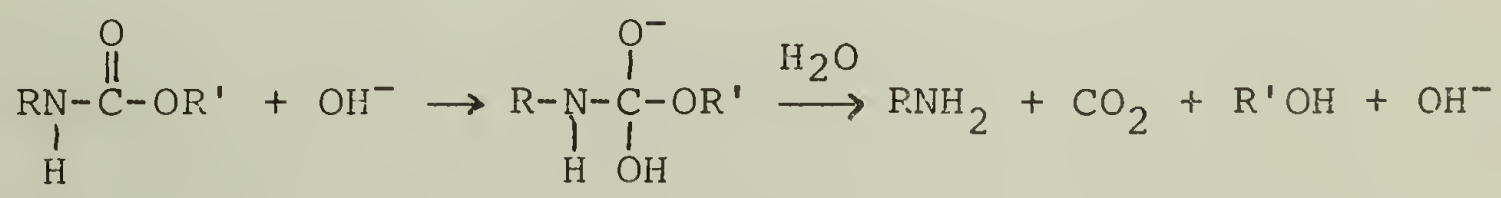
chain lengths of the aliphatic saturated dicarboxylic acids and glycols incorporated in the polyesters only had negligible effects on the rate of hydrolysis. It was found, however, that the rate of hydrolysis was affected by the structure of the chain. Ether oxygens in the glycol portions of the polyester chain (diethylene glycol in particular) enhanced the rate of hydrolysis almost twofold. The rate was considerably reduced in the case of the sterically hindered polyesters containing 2,2-dimethyl-1,3-propanediol. The activation energies for the hydrolysis (12.7-13.3 kcal/mol) agreed well with those of polyesterification reactions[73] and alkaline hydrolyses[74] determined in earlier studies.

The hydrolysis of linear polyesters[75] was found not to be dependent on the molecular weight of the polymers in the range from 550 to 16,300. The rate of hydrolysis was, however, shown to be slightly dependent on the chain length in the dicarboxylic acid component. This effect was most pronounced for the polysuccinates, in agreement with earlier work.[72]

A number of studies devoted to examining the hydrolysis of polycarbonates have been carried out.[76] Most investigations were concerned with bisphenol A polycarbonate under alkaline conditions and, as expected, polycarbonates were shown to have a tendency to hydrolyze more rapidly than the polyesters of other dicarboxylic acids.

Qualitatively, however, the hydrolysis of polycarbonates is very similar to that of polyesters.

The hydrolysis of carbamates, or urethanes, has been investigated by several workers.[77-84] All the authors agreed that N,N-disubstituted carbamates were more stable to hydrolysis than the monosubstituted derivatives. Christenson,[78] for example, found that the second-order rate constant for the alkaline hydrolysis of unsubstituted aromatic carbamates of the type ArNHCOOR, where Ar is an aromatic group, was of the order of 10^5-10^6 times that of the monomethyl-substituted carbanilates of the type $ArN(CH_3)COOR$. In addition, aromatic carbamates have been found to hydrolyze faster than aliphatic carbamates. The rate of hydrolysis decreases in the following manner: phenyl > benzyl > cyclohexyl. The higher rate of hydrolysis of the carbamates from aromatic isocyanates and benzyl-isocyanates as compared to aliphatic isocyanates has been ascribed to the greater electron donating ability of the aliphatic groups.[80] The urethane carbonyl group would thus be less prone to hydrolysis by alkaline catalysis. The hydrolysis of carbamates from aliphatic isocyanates results in the formation of the more basic aliphatic amines:



Barth and Munch[81] found meta-substituted carbanilates more susceptible to hydrolysis than ortho-substituted carbanilates and attributed this behavior to steric screening in the ortho compounds that is not a factor in the meta isomer.

These same trends toward hydrolysis have been found with the high molecular weight polyurethanes. Polyurethanes based on 2,4-toluenediisocyanate were found[80] to hydrolyze at five times the rate of polymers based on p-xylylenediisocyanate and approximately fifteen times as fast as those based on 4,4'-dicyclohexylmethane diisocyanate at 27°C. This trend is even more pronounced at 40°C. The hydrolysis of some polyurethanes in alkaline media were also found to proceed by a factor of nearly three times as fast as in acidic media. Polyester-based polyurethanes have been shown in a number of studies[82,83] to be less stable towards hydrolysis than polyether-based polyurethanes. High crosslink density has also been found to increase the resistance of polyurethanes to hydrolytic degradation.[84]

The hydrolysis of phosphate esters has been studied by a number of authors as would be expected, considering the significance of phosphate linkages in biological systems. Orthophosphoric acid, a tribasic acid, not only gives trisubstituted esters, but also di- and monosubstituted esters. Much of the literature concerning

the hydrolysis of phosphate esters has been extensively reviewed,[85] consequently this discussion will be limited to the presentation of some of the more general facets of trisubstituted phosphate ester hydrolysis.

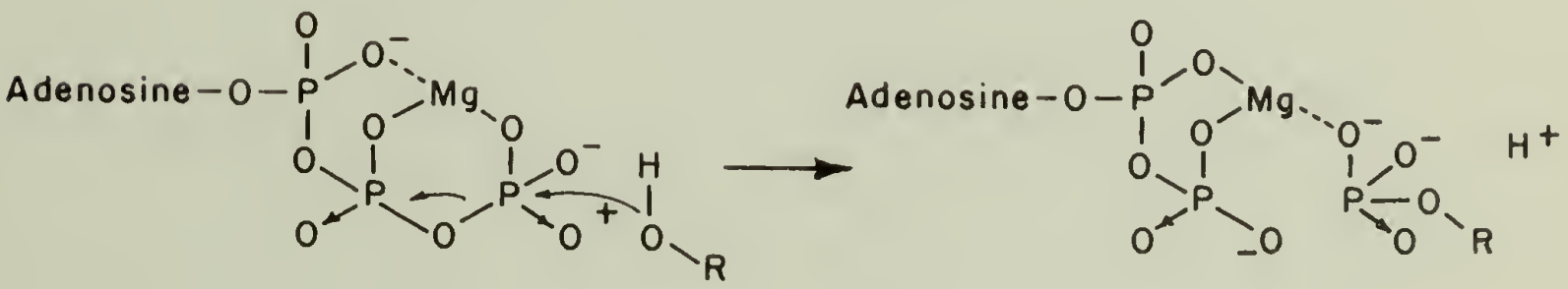
The reactions of trialkyl phosphate are simple. Nucleophiles, such as hydroxide or water, can attack either at the phosphorus or at the carbon atom of the carbon-phosphorous bond. Hydroxide, for example, attacks the phosphorous atom, while the less nucleophilic water molecule has been shown to attack the neighboring alkyl carbon.[86] Acids, as a rule, generally do not catalyze the hydrolysis of trialkyl phosphates but the mono- and dialkyl phosphates are susceptible to acid-catalyzed hydrolysis.

Triaryl phosphates, however, do undergo acid-catalyzed hydrolysis, particularly if the aryl groups contain electron withdrawing substituents such as NO_2, Cl, or CH_3CO.[87] Nitrophenyl phosphates have even been shown to be more reactive than the primary alkyl phosphates in acid hydrolysis.[88] Triaryl phosphates have been shown to be relatively unreactive with water, however, they react very readily with hard nucleophiles, with the attack taking place on the phosphorous atom.[89]

Metal ions have also been shown to influence the hydrolysis of phosphate esters. Murakami and Sunamoto[90] have postulized that this influence results from an effec-

tive charge neutralization of the substrate. They also found that chelate-forming ability is one of the most important factors for the catalytic efficiency of bivalent metal ions, such as Ni^{2+}, Cu^{2+} and Mg^{2+}. The presence of specific metal ions, particularly Mg^{2+}, in many biological reactions involving phosphates is of great importance. Many hydrolysis reactions will not proceed in the absence of Mg^{2+}. This has been demonstrated in the phosphorylation of glucose with adenosine triphosphate (ATP), for example.[91] The actual substrate is thought to be the Mg^{2+}-chelate of ATP. This can be illustrated as shown below (R-OH represents glucose):

$$\text{glucose} + \text{ATP} \xrightarrow{Mg^{2+}} \text{glucose 6-phosphate} + \text{ADP}$$



Innumerable other biological reactions are also known to be facilitated by bivalent metal ions.

V. Biological Degradation of Synthetic Polymers

Relatively little fundamental work has been done on the biological degradation of synthetic polymers. This work can be divided into two basic areas; the first is concerned with the microbial degradation of rubbers and plastics exposed to the outdoor environment during use. The second is the degradation of synthetic polymers in contact with physiological environments.

Due to the complexity of many plastic and rubber formulations, conflicting reports are often presented concerning the microbial degradation of these materials. For instance, it has been reported that polymers have been attacked when in fact it was the additives which were being attacked. Another uncertainty is the extent of degradation; the material may be described as having "failed" when in fact the attack was only superficial and the material would have been able to continue to perform as intended.

It has been reported[92-94] that purified natural rubber is susceptible to quite divergent micro-organisms. Styrene-butadiene rubber (SBR) on the other hand, has shown much less evidence of attack by micro-organisms.[95]

Similar experiences have been noted with butyl, nitrile, and polysulphide rubbers, as well as with "Hypalon," a chlorosulfonated polyethylene. Silicon rubbers are generally considered to be resistant to micro-biological attack. Polyurethane rubbers derived from polyesters or polyethers, on the other hand, have been shown to be very susceptible to degradation by a wide variety of micro-organisms. Although various investigators have reported polyvinyl chloride as being susceptible to microbial attack, it appears that it is the plasticizer in the material which is directly attacked, and not the polymer itself.[96,97] Similar results have been obtained from studies on polytetrafluoroethylene, polyvinyl alcohol, polystyrene, and poly(methyl methacrylate). A variety of conflicting reports have been presented pertaining to the susceptibility of nylons to microbial degradation.[97,98] Much of the susceptibility seems to originate from the physical form of the polymer, i.e., cable covering, film, fiber, or fabric. Many cellulose plastics, on the other hand, show surprising resistance to attack by micro-organisms, particularly the acetate and proprionate, as well as ethyl and benzyl cellulose.[99] Cellulose itself and cellulose nitrate, however, appear to be very susceptible to fungus growth. Many phenolic resins appear to be highly resistant to bacterial attack,[100] and some resorcinol-formaldehyde resins are active bacteriostats in their own right.[13]

As a rule, however, it is very difficult to predict the susceptibility of a synthetic polymer to degradation by micro-organisms. There does not seem to be any clear-cut trends, nor has it been possible up to the present time to say which chemical groups in each polymer are most susceptible.

Much of the research on the effect of physiological environments on polymers is equally difficult to assess. A number of studies on the suitability of polymers as prosthetic devices have been carried out, however, by implanting the materials in laboratory animals. From these studies a number of trends have been noted. The major route of degradation in vivo does seem to be hydrolysis, with the rate essentially controlled by the accessibility of the hydrolyzable linkage. For example, nylon 66, nylon 6, and some polyurethanes degrade at moderate rates when implanted in rats.[101,102] These polymers contain hydrophilic linkages susceptible to hydrolysis, such as $-\overset{H}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-$ and $-\overset{H}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-O-$. Polyethylene terephthalate, on the other hand, has been shown to be quite stable.[101,102] This has been attributed to the hydrophobicity of the polymer which prevents water from readily migrating to the labile ester linkages. Some polymers containing no readily apparent hydrolyzable linkages, such as polyethylene, polystyrene, and poly(methyl methacrylate), however, have shown some degradation after implantation. Surface degradation was

shown to be occurring on these polymers,[103] presumably initiated by free-radical formation. Lyman[104] has collected quantitative data on the effects of the physiological environment on a number of synthetic polymers (Table 2). Little detailed descriptions of sample histories were given, however, the data does seem to show a susceptibility towards degradation in those polymers containing labile hydrophilic linkages.

Although the degree of degradation is apparently influenced to some extent by the chemical nature of the bonds in the backbone chain, many other factors also seem to affect the rate of degradation. Among these are the degree of orientation and the crystallinity of the macromolecules in the implant, the stresses applied to the polymer, and the flux of body fluids around and through the implant. Other, as yet unknown, factors undoubtedly influence the effective lifetime of polymers in physiological environments as well.

VI. Biological Activities of Primaquine and Bithionol

A. Primaquine. It is in the area of malaria chemotherapy that primaquine finds its primary use. The disease of malaria has been known to man for thousands of years, is one of the most protracted of all infections, and requires extremely long therapy. It has been said that "in terms of

TABLE 2

EFFECT OF PHYSIOLOGICAL ENVIRONMENT ON POLYMER PROPERTIES[104]

Polymer	Effect
Polyacrylonitrile[a]	No visible degradation, 24% loss in tensile strength after 735 days
Polycaprolactam	Slowly degrades
Polydimethylsiloxane[b]	No obvious degradation
Polyethylene	No obvious degradation or fragmentation, 28% loss in tensile strength after 17 months
Poly(ethylene terephthalate)	No obvious degradation, 0 to 11% loss in tensile strength after several years
Poly(hexamethylene adipamide)	Slowly degrades, 10 to 50% loss in tensile strength over several years
Poly(methyl methacrylate)	No obvious fragmentation or degradation
Polytetrafluoroethylene	No obvious degradation, 0 to 5% loss in tensile strength, some loss in elongation
Polyurethane[c]	Softening and extensive degradation and loss of tensile strength
Polyvinyl alcohol[d]	Some erosion of sponge, shrinkage, and mineralization

[a]As the copolymer (Orlon).

[b]Dow Corning Silastic materials.

[c]Generic term; samples examined are not necessarily indicative of all members of this family.

[d]As the formalized polyvinyl alcohol sponge.

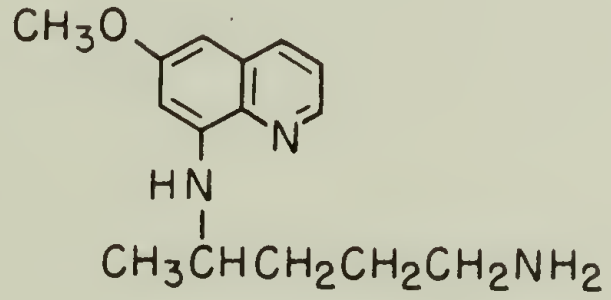
morbidity, malaria is the most important of all the ills that beset mankind."[105] Nearly one fourth of the world's population live in malaria infested regions with almost half of these in areas where eradication programs have yet to be started. Malaria takes long periods of treatment to cure and drug resistance and relapses are not infrequent.

Malaria is actually a complex of diseases resulting from the transmission of protozoa known as Plasmodia to man by the "bite" of an infected anopheline mosquito.[106] Control of malaria can be approached from the standpoint of curing the disease in man (or other mammalian host) or in the mosquito, or in eradicating the mosquito vector. Approaches to these at the practical level involve the first and last mentioned items. The present discussion will focus on the curing of the disease in man.

Treatment of malaria in man has long been known in a practical sense through administration of folk remedies such as quinine and febrifugine. These act almost exclusively on the schizonts (asexual forms of plasmodia in blood), and are known as schizontocides.[106] Synthetic antimalarials which also act on these blood forms include chloroquanide, chloroquine, amodiaquine, quinacrine, pyrimethamine, and trimethoprim. Several sulfonamides such as sulfadimethoxine and sulfalene, as well as sulfones like dapsone and acedapsone also exert schizontocidal action. Thus far, however, only 8-aminoquinoline derivatives

have shown appreciable activity against gametocytes (sexual form of malaria parasites), as well as against parasites residing in tissues.

Because malaria is a complex disease there is no single drug that can be used for its treatment, but rather drugs are usually administered in combination with one another. One of the drugs used most often is primaquine (II) (8-(4-amino-1-methylbutylamino)-6-methoxyquinoline), an 8-aminoquinoline. Although primaquine was originally synthesized in 1946,[107] it was not until 1955[108] that commercial production of the drug became possible.



II

A potent antimalarial, primaquine acts against sexual forms of the malaria infection (gametocytes) in the blood, and also against both primary and secondary exoerythrocytic (tissue) forms in man.[106] Furthermore, primaquine has sporontocidal activity, killing the sporozites which develop in the mosquito, and is currently the gametocytocide of choice, finding broad use in the field of malaria chemotherapy in combination with the

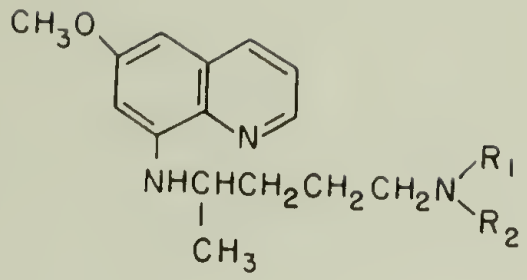
potent schizontocide, chloroquine, in the suppression and treatment of clinical malaria. The drug has been particularly effective against overt clinical attacks (or recurrences) of malaria and has marked value in combination with other agents, chloroquine in particular,[109] as both a chemoprophylactic and curative agent. The antimalarial activity of primaquine has been discussed in detail by numerous authors.[110-112]

It has been shown[113] that drugs such as primaquine (II) and pamaquine (III) bind to DNA in the form of single protonated species. Such interaction with parasite DNA has been viewed as contributory to their antimalarial activity. It has also been established[114] that primaquine has a remarkably specific effect on the mitochondria of the malaria parasite without any apparent damage to the host cell. Further contributions of primaquine and its apparent metabolic products to the entire spectrum of antiplasmodial effects are considerable, however, little detailed knowledge on much of these effects is known.

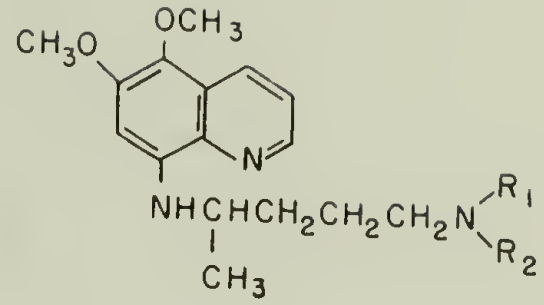
Although primaquine is effective against several forms of malaria, some resistant strains have appeared in South America and Southeast Asia.[115] This resistance, as well as the ever-present need for still more effective drugs, has prompted research into the synthesis and evaluation of several analogs of primaquine and other 8-aminoquinolines. Among all of the 8-aminoquinolines which

have distinct anti-plasmodial effects, the presence of an alkoxy or hydroxy group at position 6 is requisite.[116] An additional alkoxy function at position 5 was found to be valuable in a limited number of instances studied. This has been suggested[117,118] to be related to the formation of quinoline-5,6-quinone derivatives occurring during the metabolism of the drugs. Some of the 8-aminoquinoline derivatives that have been examined are IV-X. Several of these show considerable activity against malarial infections, but without the potency, wide activity spectrum, and relative low toxicity of primaquine.

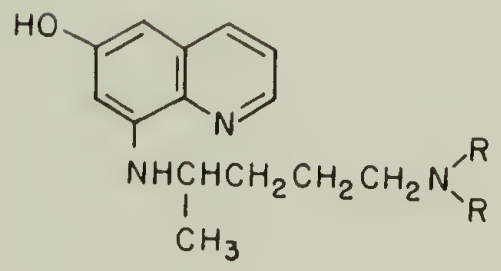
B. Bithionol. Phenol and many of its derivatives have been known to possess bacteriostatic properties for a considerable period of time. Since the discovery of the bacteriostatic properties of the 2,2'-methylenebis phenolic compounds some forty years ago, a number of compounds possessing antibacterial activity were found that showed unusual affinity towards human skin.[119-121] The most prominent of these discoveries was that of 2,2'-methylenebis(3,4,6-trichlorophenol), more popularly known by its generic name, hexachlorophene. Because of the effectiveness of this compound in suppressing undesirable microflora on the skin, extensive screening programs were conducted to try to find similar agents of high activity and low toxicity. One of the compounds screened, bithionol (XI)



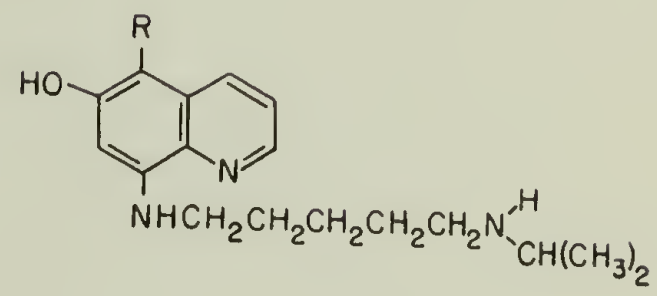
	R_1	R_2
III	C_2H_5	C_2H_5
IV	H	i-C_3H_7



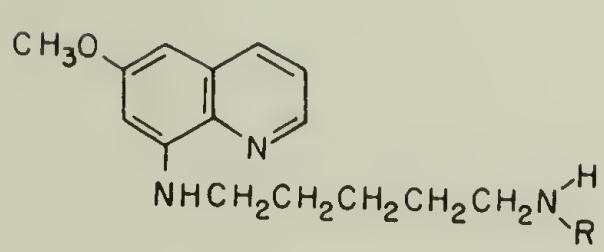
	R_1	R_2
V	H	i-C_3H_7
VI	C_2H_5	C_2H_5



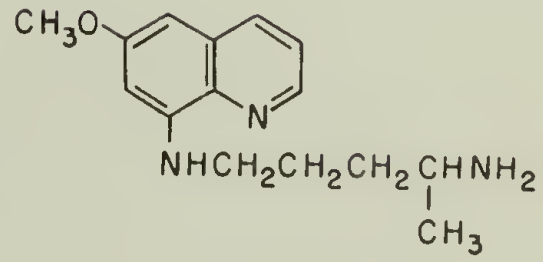
VII $R = CH_3, C_2H_5$



VIII

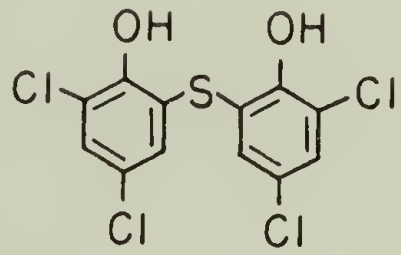


IX $R = n$-C_3H_7, i-C_3H_7



X

(2,2'-thiobis(4,6-dichlorophenol)) proved to have considerable potential as a bacteriostat and fungicide.



XI

Shumard, Beaver and Hunter[122] summarized many of the chemical, physical, and pharmacological properties of bithionol and found it to be very close in activity to hexachlorophene. Bithionol was tested in vitro for its antimicrobial activity against a wide spectrum of bacteria, and found to be consistently effective against all the gram-positive bacteria tested and frequently effective against gram-negative species as well. The growth of both Micrococcus pyogenes var. aureus, one of the most prevalent micro-organisms found in skin flora, and Corynebacterium diphtheriae, a component of the group of diphtheroids which inhabit the deep pores and hair follicles of the skin and an organism frequently associated with acneform conditions,[123] were found to be particularly inhibited by bithionol, even at dilutions of up to one to ten parts per million. The addition of soap into the test medium had no effect on the inhibiting behavior of

bithionol. When used in soap formulations at the 1 and 2 percent levels, results comparable to those obtained with hexachlorophene were found.

Barr and Moore[124] have reported bithionol to be active against a number of different bacteria found on the skin and hair of animals. Morrison[125] described the incorporation of bithionol into fibers by mixing it with polymer resins. When combined with other fibers not containing bithionol and woven into fabric, material with very long-lasting bacteriostatic properties was obtained. The use of these fabrics for hospital dressings, bandages, and the like, was suggested. Takamatsu and Murata[126] have described the preparation of a compound made from a 1:1 complex of bithionol and 4,5-diphenylimidazole that was also shown to be useful as a topical antiseptic with antihistamine action. In addition, several bisphenol phosphorous esters were made by Jungermann and Reich,[127] including those from both hexachlorophene and bithionol, and were found to be useful bacteriostats.

Shumard et al.[122] have also shown bithionol to have good activity against a number of the pathogenic species of fungus. Other authors have also reported bithionol to have antifungal activity, as well as anthelmintic properties[128] against certain types of worms and flukes in both animals and man.

A number of investigators have tried to elucidate

the mechanism by which bithionol and hexachlorophene exert their influence over micro-organisms. Although it is unconfirmed at this time, Frederick, Corner, and Gerhardt[129] have mentioned that halogenated bisphenols appear to affect the respiratory inhibition of micro-organisms at sites within the membrane-bound portion of the electron transport chain.

Although Shumard[122] reported a surprisingly low toxicity for bithionol in both oral and cutaneous applications, other studies[130] have shown the toxicity to be somewhat higher. However, on the basis of evidence indicating that bithionol was capable of causing photosensitivity and cross-sensitization with other commonly used chemicals such as certain halogenated salicylanilides and hexachlorophene, the Federal Food and Drug Administration banned its use in cosmetics intended for humans in 1967.[131] Nevertheless, the compound is still in use in many different parts of the world and is used today in the United States in many veterinary products and preparations.

VII. Preparation of Polymers From Hindered Bisphenols

Very few investigations concerning the preparation of polymers from hindered bisphenols have been undertaken. Most of the work has focused on 4,4'-bisphenol derivatives as summarized in Table 3.

TABLE 3

TRANSITION TEMPERATURES OF POLYCARBONATES FROM BISPHENOLS[a]

Bisphenol	Glass Transition Temperature, °C	Softening Temperature, °C
2,2-bis(4-hydroxyphenyl)propane		220-230
2,2-bis(4-hydroxy-3-methylphenyl) propane		150-170
2,2-bis(4-hydroxy-3-chlorophenyl) propane		190-210
2,2-bis(4-hydroxy-3,5-dichlorophenyl) propane		250-260
2,2-bis(4-hydroxy-3,5-dibromophenyl) propane		253-263
bis(4-hydroxyphenyl)sulfide		220-240
bis(4-hydroxy-3-methylphenyl)sulfide		200-210
2,2-bis(4-hydroxyphenyl) norbornane	224	
2,2-bis(4-hydroxy-3-methylphenyl)norbornane	161	
2,2-bis(4-hydroxy-3-chlorophenyl)norbornane	200	
2,2-bis(4-hydroxy-3,5-dichlorophenyl)norbornane	290	
2,2-bis(4-hydroxy-3,5-dibromophenyl)norbornane	283	
2-norbornyl-bis(4-hydroxyphenyl)methane	207	
2-norbornyl-bis(4-hydroxy-3,5-dichlorophenyl)methane	270	

TABLE 3 (cont.)

Bisphenol	Glass Transition Temperature, °C	Softening Temperature, °C
5,5-bis(4-hydroxyphenyl)-4,7-methanohexahydroindane	256	
5,5-bis(4-hydroxy-3-methylphenyl)-4,7-methanohexahydroindane	217	
5,5-bis(4-hydroxy-3,5-dichlorophenyl)-4,7-methanohexahydroindane	281	
2,2-bis(4-hydroxyphenyl)-1,4-exo-5,8-endo-dimethanodecahydronaphthalene	273	
2,2-bis(4-hydroxy-3-methyl)-1,4-exo-5,8-endo-dimethanodecanhydronaphthalene	232	

(a) Compiled from references 132-135.

Schnell[132,133] synthesized a number of polycarbonates from phosgene and substituted 2,2-bis(4-hydroxyphenyl)propane (bisphenol A). He found that the polycarbonate made from 2,2-bis(4-hydroxy-3-methylphenyl) propane has a softening temperature of 150-170°C, while that from bisphenol A had a softening temperature of 220-230°C. Apparently the relatively bulky methyl group introduced more free volume into the polymer and decreased the temperature at which there was a significant onset of molecular motion in the polymer chains. If a chlorine atom replaced the methyl group, the resulting polycarbonate exhibited a softening temperature of 190-210°C, above that of the methylated derivative, but still 30° below that of bisphenol A polycarbonate. The polycarbonate from 2,2-bis(4-hydroxy-3,5-dichlorophenyl)propane, however, showed a softening temperature of 250-260°C, 60° higher than the monochloro derivative and 30° higher than the bisphenol A polymer. Substituting bromine atoms in the 3- and 5-positions in place of the chlorine atoms raised the softening temperature only slightly to 253-263°C. This can be attributed to both symmetry and steric considerations.

Similar behavior has been observed for polycarbonates made from bis(4-hydroxyphenyl)sulfide[132,133] and bis(4-hydroxy-3-methylphenyl)sulfide.[134] The later polycarbonate has a softening temperature 20-30° lower than the former (200-210°C vs. 220-240°C). No data is available

concerning mono- or disubstituted halo-derivatives.

In 1963 Jackson and Caldwell[135] studied the glass transition temperatures (T_g's) of polycarbonates made from phosgene and bisphenols derived from norbornane and related structures. They reported a T_g of 224°C for the polymer made from 2,2-bis(4-hydroxyphenyl)norbornane. Substituting a methyl group in the 3- position lowered the T_g to 161°C. The polycarbonate from the 3-chloro derivative had a T_g of 200°C, that from the 3,5-dichloro derivative a T_g of 290°C, and the polycarbonate from the 3,5-dibromo derivative a T_g of 283°C. The trends exhibited in this series are essentially the same as those observed in the series of polycarbonates based on bisphenol A. The decrease in T_g going from the dichloro to the dibromo derivative was not thought to be significant.

The same authors[135] also examined polycarbonates made from 2-norbornyl-bis(4-hydroxyphenyl)methane and 2-norbornyl-bis(4-hydroxy-3,5-dichlorophenyl)methane. Glass transition temperatures of 207 and 270°C respectively, a difference of 63°, were reported, but a difference of only 25°C was observed in the T_g's of the polycarbonates made from 5,5-bis(4-hydroxyphenyl)-4,7-methanohexahydroindane (T_g = 256°C) and 4,4-bis(4-hydroxy-3,5-dichlorophenyl)-4,7-methanohexahydroindane (T_g = 281°C) was reported. The polycarbonate made from the 3-methyl derivative had a T_g of 217°C. In addition, a difference of 41° was exhibited

between the T_g's of the polycarbonates made from 2,2-bis(4-hydroxyphenyl)-1,4-exo-5,8-endo-dimethanodecahydronaphthalene and its 3-methyl derivative (273°C and 232°C, respectively). All of the above mentioned polycarbonates were synthesized by standard stirred interfacial techniques and all had inherent viscosities of at least 0.4 dl/g.

The polyterephthalates made from bisphenol A[136] and 2,2-bis(4-hydroxy-3-methylphenyl)propane,[137] on the other hand, displayed softening temperatures of 350°C and 150-195°C respectively. The loss of symmetry and the increase in free volume seem to have played a significantly greater role in the T_g of polyterephthalates than in the polycarbonates.

Morgan[138] synthesized a series of polyesters from substituted phthaleins and isophthaloyl chloride by an interfacial process and obtained differences in polymer melt temperatures (PMT's) as shown in Table 4 below:

TABLE 4

POLYMER MELT TEMPERATURES OF POLYISOPHTHALATES FROM SUBSTITUTED PHTHALEINS

Bisphenol	Polymer Melt Temperature, °C
Phenolphthalein	355
3',3",5',5"-Tetrachlorophenolphthalein	300
3',3",5',5"-Tetrabromophenolphthalein	326
3',3",5',5"-Tetraiodophenolphthalein	> 400 (dec)

It is clear from this data that substitution in the 3 and 5 positions of the phenol groups disrupts the packing of the chains and causes a sharp decrease in the PMT. As the size of the substituents increases, the chain becomes stiffer for steric reasons, but it is not until the tetraiodo derivative is reached that the stiffness of the chain is sufficient to raise the PMT to a point where the loss in chain orientation and packing present in the unsubstituted polymer is counterbalanced.

Conix and Laridon[139,140] synthesized a number of aromatic polysulfonates based on methyl-substituted derivatives of bis(4-hydroxyphenyl)methane and 4,4'-biphenyldisulfonyl chloride. They found that the softening temperature of the polymers increased from 111-118°C for the unsubstituted polymer to 114-120°C for the polymer substituted in the 3-methyl position.[139] The greatly hindered 3,5-dimethyl substituted polymer had a further increased softening temperature of 140-170°C, while the softening temperature for the unsymmetrically substituted 2,5-dimethyl polymer dropped to 100-105°C.[140]

C H A P T E R I I

EXPERIMENTAL SECTION

I. Materials

The following chemicals were obtained from the sources indicated.

acetone	F	dimethyl sebacate	PB
acetonitrile	E	dimethyl sulfoxide	E
adipic acid	E	diphenylcarbonate	A
adipoyl chlorine	A	diphenyl ether	E
aluminum chloride	F	ethanol	F
benzene	F	ethylenediamine	A
bis(2-hydroxyphenyl) methane	A	ethylene glycol	E
1,4-butanediamine	A	fumaryl chloride	A
1,4-butanediol	A	n-heptane	F
calcium hydride	F	n-hexane	F
calcium hydroxide	F	1,6-hexanediamine	A
carbon tetrachloride	F	1,6-hexanediol	A
Carbowax PEG 400	F	hydroquinone	A
Carbowax PEG 600	F	isophthaloyl chloride	A
Carbowax PEG 1000	F	isopropylidenediphenol	A
Carbowax PEG 4000	F	2,6-lutidine	E
chloroform	F	malonyl chloride	A
chlorosulfonic acid	E	methanol	F
collidine	E	4,4'-methylenebis(6-tert-butyl-o-cresol)	PB
1,10-decanediamine	A	2,2'-methylenebis(6-tert-butyl-p-cresol)	PB
1,10-decanediol	A	methylene chloride	F
dibutyltindilaurate	PB	methylenedianiline	A
2,4-dichlorophenol	A	molecular seives (3A)	MCB
dichlorophenylphosphine	A	oxalyl chloride	A
N,N-diethylaniline	E	n-pentane	F
diethyl oxalate	A	phenyldichlorophosphate	A
4,4'-diisocyanatodiphenyl-methane	E	m-phenylenediamine	A
1,6-diisocyanatohexane	A	p-phenylenediamine	A
dimethylacetamide	A	phenylphosphoric dichloride	A
dimethylformamide	A	phosgene	MCB
dimethyl isophthalate	A		

phthalic anhydride	E	succinyl chloride	A
piperazine	A	sulfolane	E
polyepichlorohydrin	H	sulfur dichloride	PB
potassium biphthalate	F	terephthaloyl chloride	A
potassium phosphate, monobasic	F	tetrabutylammonium bromide	E
primaquine diphosphate	A	tetraethylene glycol	E
1,3-propanediamine	A	tetrahydrofuran	F
1,3-propanediol	A	4,4'-thiobis(6-tert-butyl-m-cresol)	PB
pyridine	E	4,4'-thiobis(6-tert-butyl-o-cresol)	PB
quinoline	E	toluene	F
resorcinol	M	2,4-toluenediisocyanate	A
sebacyl chloride	E	tributylamine	A
sodium bicarbonate	F	triethylamine	E
sodium carbonate (anhydrous)	F	triethylenediamine	A
sodium dodecyl sulfate	E	trifluoroacetic acid	A
sodium hydroxide	F	trifluoroacetic anhydride	A
sodium phosphate, dibasic	F	zinc oxide	F

Sources: A = Aldrich Chemical Co.; B = J.T. Baker Chemical Co.; E = Eastman Organic Chemicals; F = Fisher Scientific Co.; H = Hercules, Inc.; M = Mallinkrodt Chemical Works; MCB = Matheson, Coleman and Bell; PB = Pfaltz and Bauer, Inc.

II. Purification of Solvents and Reagents

Distillations were carried out using a 30 cm Vigreux column equipped with a variable reflux ratio distillation head. Reduced pressure distillations were carried out with magnetic stirring and a Cartesian-type diver manostat.

Acetone was distilled (bp 56°C) and stored over molecular sieves.

Acetonitrile was distilled (bp 81.5°C) from phosphorous pentoxide and stored over molecular sieves.

Benzene was distilled (bp 80°C) from a potassium-sodium alloy (approx. 50/50 by wt) and stored over molecular sieves.

Bis(2-hydroxyphenyl)methane was recrystallized twice from dry hexane and dried at 0.1 mm for 24 hr at room temperature.

1,4-Butanediamine was distilled (bp 79.0-9.5°C/20 mm) and stored over molecular sieves.

1,4-Butanediol was distilled (bp 143-4°C/20 mm) and stored over molecular sieves.

Carbowax PEG's 400, 600, 1000, and 4000 were dried at 40-50°C over phosphorous pentoxide at 1 mm for 2 weeks. They were stored at room temperature over phosphorous pentoxide at 20 mm.

Chloroform was washed 3 times with equal volumes of water, dried over $CaCl_2$, then distilled (bp 61°C) and stored over molecular sieves.

Collidine was distilled (bp 67°C/30 mm) from a sodium-potassium alloy (approx. 50/50 by wt) and stored over molecular sieves.

1,10-Decanediamine (bp 88-9°C/0.05 mm) and 1,10-decanediol (bp 118-20°C/0.05 mm) were distilled.

N,N-Diethylaniline was dried by stirring over molecular sieves for 48 hr prior to use.

Diethyl oxalate was dried over molecular sieves for 24 hr, then distilled (bp 99-100°C/20 mm).

Dimethylacetamide (DMAc) (bp 58-9°C/14 mm) and dimethylformamide (DMF) (bp 79°C/38 mm) were distilled from calcium hydride and stored over molecular sieves.

Dimethylisophthalate was recrystallized twice from water and dried at 0.01 mm over phosphorous pentoxide at 56°C for 48 hr.

Dimethylsebacate was distilled (bp 128°C/0.1 mm) and stored at 40-50°C over molecular sieves.

Dimethyl sulfoxide (DMSO) was distilled (bp 88°C/20 mm) from calcium hydride and stored over molecular sieves.

Diphenyl carbonate was recrystallized twice from 95% ethanol and dried over calcium chloride at 20 mm for 72 hr.

Ethylenediamine was fractionally distilled (bp 119-20°C) from metallic sodium and stored over molecular sieves.

Ethylene glycol (bp 118-9°C/20 mm), 1,6-hexanediamine (bp 108-9°C/20 mm), and 1,6-hexanediol (bp 134-6°C/10 mm) were distilled and stored over molecular sieves.

Isophthaloyl chloride was recrystallized twice from dry hexane and dried over calcium chloride at 20 mm for 48 hr.

Isopropylidenediphenol was recrystallized twice from toluene and dried for 24 hr over phosphorous pentoxide

at 100°C and 20 mm.

4,4'-Methylenebis(6-tert-butyl-o-cresol) and 2,2'-Methylenebis(6-tert-butyl-p-cresol) were each recrystallized twice from toluene and dried at 0.1 mm for 24 hr.

Methylene chloride was stirred over calcium chloride for 6 hr, then distilled (bp 39.8°C) and stored over molecular sieves.

Methylenedianiline was recrystallized twice from water and dried for 4 days at 0.01 mm over phosphorous pentoxide.

Methylenediisocyanate was distilled (bp 165-6°C/0.1 mm) immediately before use.

m-Phenylenediamine was recrystallized three times from dry benzene and dried at room temperature over calcium chloride at 20 mm.

p-Phenylenediamine was sublimed twice (80°C/3 mm) from activated charcoal and stored under nitrogen.

Piperazine was sublimed twice at 65°C and 3 mm and stored over calcium chloride.

Polyepichlorohydrin was precipitated twice into methanol from 3% DMAc solutions. The precipitated polymer was washed with methanol and dried for 72 hr at 0.01 mm over phosphorous pentoxide.

1,3-Propanediamine (bp 55°C/20 mm) and 1,3-propanediol (bp 126°C/20 mm) were distilled and stored over

molecular sieves.

Pyridine (bp 113-4°C) and quinoline (bp 122-3°C/20 mm) were distilled from metallic sodium and stored over molecular sieves.

Sulfolane was stirred over sodium hydroxide for 24 hr, then distilled (bp 175-6°C/0.5 mm) directly onto molecular sieves. After 24 hr the material was redistilled (bp 119.0°C/0.05 mm) and stored over molecular sieves at 40-50°C.

Terephthaloyl chloride was recrystallized twice from n-hexane and dried over phosphorous pentoxide at 0.1 mm for 48 hr.

Tetraethylene glycol was stirred over molecular sieves for 7 days, then distilled (bp 170°C/1 mm) and stored over molecular sieves.

4,4'-Thiobis(6-tert-butyl-m-cresol) and 4,4'-thiobis(6-tert-butyl-o-cresol) were each recrystallized twice from dry toluene and dried at 0.1 mm for 24 hr at room temperature.

Toluene (bp 110°C), tributylamine (bp 111-2°C/13 mm), and triethylamine (bp 87°C) were distilled from a sodium/potassium alloy (approximately 50/50 by weight).

Triethylenediamine was sublimed twice under nitrogen at 60°C and stored under nitrogen.

All other solvents and reagents were used as received.

III. Polymerization of Primaquine

A. Isolation of primaquine. Primaquine diphosphate was dissolved in distilled water to make an approximately 5 wt% solution. To this solution was slowly added twice the volume of 10% aqueous sodium carbonate necessary to neutralize the phosphate. The dark oil that separated was extracted with 3 equal volume portions of chloroform. The combined organic layers were dried over calcium chloride and filtered. Pure primaquine could be isolated from the clear yellow solution by evaporation of the solvent under nitrogen, followed by distillation (bp 161-4°C/0.01 mm). The infrared spectrum (neat) showed absorptions centered around 3390 cm^{-1} (N-H stretching) and 2950 cm^{-1} (C-H stretching). See p. 218. The ^{1}H NMR spectrum (neat) showed peaks at δ 1.0-2.1 (aliphatic protons, 10 H), 3.8 ($C\underline{H}_3O$, 3H), 3.6 and 6.2 (amine protons, 3 H), and 7.0-8.0 (aromatic protons, 5 H). See p. 204.

B. Reaction of primaquine with difunctional intermediates using one-step polymerization techniques.

1. Reaction of primaquine with sebacyl chloride - Procedure I. A 50 ml round-bottomed flask was charged with primaquine (0.29g, 1.1 mmole), calcium hydroxide (0.51g, 6.9 mmole), and chloroform (11 ml). To this mixture was added 0.27g (1.1 mmole) of sebacyl chloride in 11 ml of chloroform over 5 min with stirring. The mixture

was stirred for 14 hr, filtered, and concentrated under a nitrogen stream to a sticky yellow solid with an inherent viscosity of 0.03 dl/g (0.1% in $CHCl_3$). The infrared spectrum of the oil showed absorbtions at 3360-3330 cm^{-1} (amide N-H stretching), 1645 cm^{-1} (C=O stretching), and 1560 cm^{-1} (N-H bending).

ANAL. calcd. for $C_{40}H_{56}N_6O_4$: C, 70.14%; H, 8.24%; N, 12.27%. Found: C, 70.21%; H, 8.29%; N, 12.08%.

- Procedure II. A 50 ml round-bottomed flask was charged with primaquine (0.28g, 1.1 mmole), calcium hydroxide (0.51g, 6.9 mmole), and chloroform (13 ml). The resulting solution was brought to reflux and 0.26g (1.1 mmole) of sebacyl chloride in 15 ml of chloroform was added over 30 min. Stirring and reflux were continued for 13 hr after which the reaction mixture was filtered. The filtrate was then reduced under vacuum to a yellow oil possessing an inherent viscosity of 0.04 dl/g (0.1% in $CHCl_3$). The infrared spectrum was identical to that described in Procedure I.

- Procedure III. A one quart Waring blender was charged with primaquine (1.79g, 6.9 mmole), sodium dodecyl sulfate (0.28g, 1.0 mmole), and sodium carbonate (1.47g, 13.8 mmole) dissolved in 150 ml of water. To the rapidly stirred solution in the blender was added 1.65g (6.9 mmole) of sebacyl chloride in 35 ml chloroform. Residual sebacyl chloride was washed into the blender with an additional

5 ml of chloroform. Stirring at high speed was continued for 30 min after which the emulsion was broken by the addition of 2 ml of concentrated HCl. The chloroform layer was separated and concentrated under reduced pressure to a clear oil of inherent viscosity 0.02 dl/g (0.1% in $CHCl_3$). The infrared spectrum of the oil was identical to that described in Procedure I.

2. Reaction of primaquine with 1,6-diisocyanatohexane. To a solution of primaquine (0.30g, 1.2 mmole) in chloroform (10 ml) was added 1,6-diisocyanatohexane (0.20g, 1.2 mmole) in chloroform (10 ml). The resultant solution was stirred at room temperature for 17 hr to give a mass of fine white crystals suspended in a yellow solution. These were filtered, washed with chloroform, and air dried. The clear filtrate was concentrated under vacuum to give a yellow oil of inherent viscosity 0.02 dl/g (0.1% in $CHCl_3$). The oil had an infrared spectrum that displayed absorbtions at 3430 and 3320 cm^{-1} (N-H stretching) and at 1620 and 1580 cm^{-1} (C=O stretching). The dried crystals showed absorbtions at 2270 cm^{-1} (N=C=O stretching), 1640 and 1600 cm^{-1} (C=O stretching), and 810 cm^{-1}.

C. Synthesis of phthalimido primaquine. A 500 ml round-bottomed flask equipped with a continuous extraction apparatus (charged with 3A molecular sieves), condenser, and magnetic stirrer was charged with 10.9g (42.0 mmole) of

primaquine, 6.2g (42.0 mmole) of phthalic anhydride, 0.43g (4.2 mmole, 0.59 ml) of triethylamine, and 200 ml of benzene. The mixture was refluxed 3 hr, during which the refluxing solvent was allowed to pass through the molecular sieves in the extraction apparatus. The hot solution was then filtered into a 3000 ml round-bottomed flask, where 900 ml of benzene, 800 ml of water, and 60 ml of 48% hydrobromic acid were added, and the mixture again heated to reflux with stirring. The mixture was quickly poured into a warm 3000 ml separatory funnel. The organic layer was separated, dried with calcium chloride, filtered, and reduced under vacuum to an oil. The crude product was dissolved in 600 ml of methanol at 62°C and allowed to cool slowly. After 24 hr at 0°C 9.11g (46%) of bright yellow phthalimido primaquine crystals (mp 91-2°C) could be separated. The mother liquor was concentrated and the recrystallization procedure repeated 3 more times to give a total of 11.3g (69%) of material. The infrared spectrum (KBr) showed absorbtions centered at 3400 cm^{-1} (N-H stretching), 2940 cm^{-1} (C-H stretching), and 1710 cm^{-1} (C=O stretching). See p. 218. The ^{1}H NMR spectrum (CCl_4) showed δ 1.0-2.1 (aliphatic protons, 10H) 3.8 ($C\underline{H}_3O$, 3H) and 6.9-8.6 (aromatic protons, 9H). See p. 204.

ANAL. calcd. for $C_{23}H_{23}N_3O_3$: C, 70.93%; H, 5.95%. Found: C, 70.88%; H, 6.14%.

D. Preparation of primaquine biuret polymers.

1. Primaquine/1,6-diisocyanatohexane biuret polymer. An eight inch test tube was charged with 1.55g (6.0 mmole) of primaquine, 0.01g (0.1 mmole) of triethylenediamine, 0.05 ml (0.05g, 0.1 mmole) of dibutyltindilaurate, and 10 ml of DMSO. 1,6-Diisocyanatohexane (1.00g, 6.0 mmole) in DMSO (10 ml) was added to the solution in one portion. The mixture, which warmed slightly, was stirred for 1 hr at room temperature and then for 12 hr at 100°C. The moderately viscous solution was then cooled and precipitated into 200 ml of water to give a tacky solid which was redissolved in 20 ml of chloroform and precipitated into 200 ml of methanol. The resulting beige powder weighed 0.64g (25%) and had an inherent viscosity of 0.10 dl/g (0.5% in DMSO). The infrared spectrum showed absorbtions at 3350 cm^{-1} (N-H stretching), 2930 and 2850 cm^{-1} (C-H stretching) and 1750 cm^{-1} (C=O stretching). See p. 219.

ANAL. calcd. for $C_{23}H_{33}N_5O_3$: C, 64.61%; H, 7.78%. Found: C, 64.57%; H, 7.71%.

This procedure was repeated several times using DMF, DMAc, and sulfolane in place of DMSO. The results from these experiments are shown in Table 5.

2. Primaquine/4,4'-diisocyanatodiphenylmethane biuret polymer. Primaquine (1.75g, 6.8 mmole), triethylenediamine (0.01g, 0.1 mmole), and dibutyltindilaurate (0.05 ml, 0.05g, 0.1 mmole) in DMSO (10 ml); 4,4'-diisocyanato-

diphenylmethane (1.69g, 6.8 mmole) in DMSO (10 ml); yield: 2.93g (85%); inherent viscosity: 0.07 dl/g (0.5% in DMSO); infrared spectrum: 3350 cm^{-1} (N-H stretching), 2930 cm^{-1} (C-H stretching), and 1760 cm^{-1} (C=O stretching). See p. 219.

ANAL. calcd. for $C_{30}H_{31}N_5O_3$: C, 70.76%; H, 6.13%; N, 13.74%. Found: C, 70.30%; H, 6.32%; N, 13.48%.

This procedure was repeated several times using DMF, DMAc, and sulfolane in place of DMSO. The results from these experiments are shown in Table 5.

3. Primaquine/1,6-diisocyanatohexane/4,4'-diisocyanatodiphenylmethane biuret copolymer. A 50 ml round-bottomed flask was charged with primaquine (1.89g, 7.3 mmole) and DMSO (10 ml). 1,6-Diisocyanatohexane (0.61g, 3.6 mmole) in DMSO (10 ml) was added and the resultant solution was stirred for 90 min at room temperature. The solution was warmed to 90°C and 0.01g (0.1 mmole) of triethylenediamine and 0.06 ml (0.06g, 0.1 mmole) of dibutyltindilaurate in 1 ml of DMSO was added, followed by 0.91g (3.6 mmole) of 4,4'-diisocyanatodiphenylmethane in 10 ml of DMSO. The reaction mixture was stirred at 90°C for 6 hr, after which it was cooled and poured into 250 ml of water to give 2.88g (85%) of a pale yellow polymer with an inherent viscosity of 0.12 dl/g (0.5% in DMSO). The infrared spectrum showed absorbtions at 3350 cm^{-1} (N-H stretching), 2930 and 2850 cm^{-1} (C-H stretching), and 1760 cm^{-1}

(C=O stretching). See p. 220. The ^{1}H NMR spectrum (d_6-DMSO) showed δ 0.7-4.3 (aliphatic, amide, and methoxy protons, 45), 5.9-6.7 (amide protons, 3), and 6.7-8.7 (aromatic protons, 11). See p. 205.

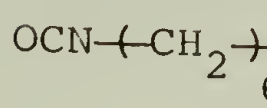
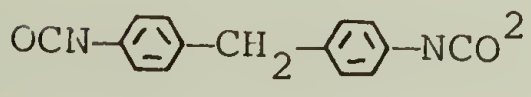
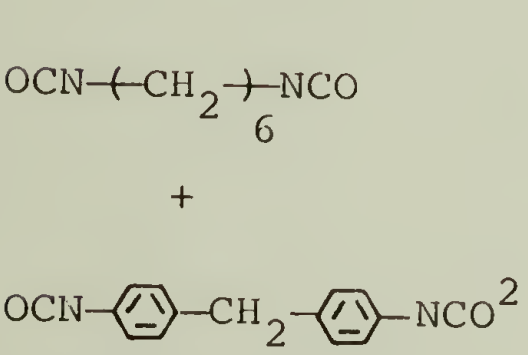
ANAL. calcd. for $C_{53}H_{64}N_{10}O_6$: C, 67.42%; H, 6.88%; N, 14.95%. Found: C, 67.90%; H, 7.10%; N, 14.56%.

This procedure was repeated using DMF in place of DMSO. The results from these experiments are shown in Table 5.

E. Preparation of primaquine-substituted polyepichlorohydrin. Each of four 8 inch test tubes was charged with polyepichlorohydrin (0.70g, 7.6 mmole) and DMAc (12 ml). After the polymer had dissolved (approximately 16 hr), the desired amount of primaquine was added to each of the four solutions as described in Table 6. The solutions were left for 10 days at room temperature, after which each was precipitated into 150 ml of methanol. The yield and chlorine content were determined after drying the resulting beige colored elastomers for 48 hr at 0.01 mm. The degree of substitution was calculated from the ratios of the integrated signal intensities of the aromatic protons to those of the $C\underline{H}_2C\underline{H}_2O$ protons. The infrared spectra of each of the products were similar with absorbtions at 3390 cm^{-1} (N-H stretching), 2950 and 2900 cm^{-1} (C-H stretching), and 1115 cm^{-1} (C-O stretching). The ^{1}H NMR spectra were also similar

TABLE 5

PREPARATION OF PRIMAQUINE BIURET POLYMERS

Isocyanate Used	Yield (%)	η_{inh}[1] (dl/g)	Solvent
	20-85	0.03-0.08	DMF, DMAc
	25-50	0.07-0.10	DMSO, Sulfolane
	30-75	0.02-0.06	DMF, DMAc
	85-95	0.05-0.07	DMSO, Sulfolane
 [3]	50	0.05	DMF
	85	0.12	DMSO

[1] 0.5% in DMSO

[2] One-step reaction

[3] Two-step reaction

TABLE 6

PREPARATION OF PRIMAQUINE-SUBSTITUTED POLYEPICHLOROHYDRIN

Experiment	Polyepichloro-hydrin in g (in mmole)	Primaquine in g (in mmole)	Yield in g	Chlorine Content in wt %	Degree of Substitution in mole %
1	0.70 (7.6)	0.98 (3.8)	0.67	20.08	25
2	0.70 (7.6)	1.97 (7.6)	0.64	12.34	45
3	0.70 (7.6)	2.93 (11.3)	0.69	7.81	70
4	0.70 (7.6)	4.88 (18.8)	0.68	3.10	95

with peaks at δ 1.0-2.4 (aliphatic protons), 3.4-4.1 ($C\underline{H}_2C\underline{H}_2O$, $C\underline{H}_2Cl$, and $C\underline{H}_3O$), and 7.0-8.5 (aromatic protons).

IV. Preparation of Bithionol and Bithionol Polymers

A. Bithionol. The following procedure is a modification of the one used by Cooper.[141] A 5000 ml round-bottomed flask was charged with 2000g (12.3 mole) of 2,4-dichlorophenol and 62g (0.46 mole) of anhydrous aluminum chloride and brought to 64°C. Sulfur dichloride (515 ml, 820g, 8.0 mole) in carbon tetrachloride (2250 ml) was added to the melt with vigorous stirring over 6 hr. The rate of addition of the sulfur dichloride solution had to be regulated so that the reaction did not become unmanageable. The temperature of the reaction mixture rose to 75°C during the addition and a considerable amount of precipitate formed. The color of the reaction mixture changed from a greenish shade during the time of the initial addition of sulfur dichloride to a blue color in the later stages of the addition. The thick mixture was stirred for 3 hr after the addition of the sulfur dichloride had been completed, then the reaction was stopped by the addition of 1000 ml of water, which caused the reaction mixture to turn a bright yellow color. After stirring an additional 20 min, the mixture was filtered and the precipitate washed repeatedly with several portions of 70% ethanol. The pale green solid was

dissolved in 4000 ml of a boiling toluene/ethanol solution (60/40 vol/vol) and cooled to give 775g (35%) of colorless crystals (mp 185-8°C). The mother liquor was concentrated to 1400 ml and cooled, affording an additional 170g (8%) of crystals (mp 184.5-8.0°C). Bithionol was recrystallized twice from toluene/ethanol to give polymerization grade material (mp 187-8°C). The infrared spectrum (KBr) showed absorbtions at 3400 and 3340 cm^{-1} (O-H stretching) and 1450 cm^{-1} (C-C vibration). See p. 220. The ^{1}H NMR spectrum (d_6-acetone) showed absorbtions at δ 8.1 (O<u>H</u>, 2H) and 7.2 and 7.4 (aromatic protons, 4H). See p. 205. The ultraviolet spectrum (aqueous pH 10.0) showed maxima at 318 and 226 mm with molar extinction coefficients of 1.58×10^4 and 6.75×10^4 liter·mole^{-1}·cm^{-1}, respectively.

<u>B. Bithionol bischloroformate and bithionol carbonate bischloroformate</u>. The following recipe is a modification of a procedure used by Osper, Broker, and Cook.[142] Approximately 750 ml (790g, 8.0 mole) of liquid phosgene was transferred from a liquified gas cylinder to a 3000 ml round-bottomed flask that had been previously cooled to -17°C with salt ice. Bithionol (712g, 2.0 mole) and toluene (2000 ml) were added to the flask and N,N-diethylaniline (600g, 4.0 mole) was added to the bithionol/phosgene suspension over 2 hr. Stirring was continued for an additional hour, after which unreacted phosgene was removed with

the aid of an aspirator. When most of the phosgene had been removed, the mixture was warmed to 40°C and a 20 mm vacuum was applied for 14 hr to remove the last traces of phosgene. Ether (1000 ml) was added and the thick suspension was filtered with suction. A clear pale yellow etheral filtrate was obtained which was concentrated to a viscous oil under reduced pressure. The oil was dissolved in 650 ml of boiling n-hexane and the solution was slowly cooled to room temperature to yield 53g (6%) of colorless crystals (mp 174-9°C). Subsequent analysis showed these crystals to be pure bithionol carbonate bischloroformate. The infrared spectrum displayed an absorbtion centered around 1805 cm^{-1} (C=O stretching). See p. 221. The ^{1}H NMR spectrum showed peaks from δ 7.0-7.4 (aromatic protons). See p. 206.

ANAL. calcd. for $C_{27}H_8Cl_{10}O_7S_2$: Cl, 41.08%. Found: Cl, 40.96%.

After removing the bithionol carbonate bischloroformate crystals, the mother liquor was again concentrated under reduced pressure to a viscous oil which was left at room temperature in a sealed flask. After 8 days spontaneous crystallization of the material was observed. Crystal growth continued until the entire contents of the flask was a solid mass. The crystals were then removed and vacuum filtered while the whole operation was carefully protected from moisture. The yield of crude bithionol bischloro-

formate (mp 65-71°C) was 431g (45%). Recrystallization from 1000 ml boiling n-pentane gave 380g (40%) of bithionol bischloroformate (mp 70-2°C). The infrared spectrum showed an absorbtion at 1780 cm^{-1} (C=O stretching). See p. 221. The ^{1}H NMR spectrum showed peaks at δ 7.1 and 7.3 (aromatic protons). See p. 206.

ANAL. calcd. for $C_{14}H_4Cl_6O_4S$: C, 34.96%; H, 0.84%; Cl, 44.23%. Found: C, 35.02%; H, 0.83%; Cl, 44.76%.

The identity of both bithionol bischloroformate and bithionol carbonate bischloroformate was confirmed by reacting each of the compounds with an excess of dry methanol for 24 hr at room temperature. A 95 and 100% yield of the respective dimethyl esters were obtained. The ^{1}H NMR spectrum of bithionol bis(methyl carbonate) showed peaks at δ 3.8 (CH_3, 6H) and 7.1 and 7.3 (aromatic protons, 4H). See p. 207. The spectra of bithionol carbonate bis(methyl carbonate) showed peaks at δ 3.9 (CH_3, 6H) and 6.9 and 7.3 (aromatic protons, 8H). See p. 207.

NOTE: Strict safety precautions should be observed when working with phosgene as it is highly toxic! Work should be conducted in an efficient fume hood with suitable gas masks available for all personnel in the area. Leaks may be detected by generating ammonia vapors (from concentrated ammonium hydroxide) near the apparatus (white fumes will appear near leak sites). As an additional precaution phosgene test paper can be made by soaking filter paper in

an alcoholic or carbon tetrachloride solution containing 10% of a mixture of equal parts of p-dimethylaminobenzaldehyde and colorless diphenylamine, then drying. Exposure of this paper to approximately the maximum allowable concentration of phosgene will turn its color from a pale yellow to a darker yellow, then orange within a few minutes. The paper should be prepared fresh for each use and stored in tightly sealed brown bottles. Both of these methods for the detection of phosgene should be used whenever the presence or generation of this gas is possible or suspected. For additional information refer to the Matheson Gas Data Book.[143]

C. Bithionol polycarbonate - Procedure I. A 250 ml round-bottomed flask was charged with bithionol (3.56g, 10.0 mmole), tetrabutylammonium bromide (0.08g, 0.3 mmole), sodium hydroxide (0.81g, 20.2 mmole), water (50 ml), and methylene chloride (5 ml) and stirred to dissolve all of the reactants. A solution of bithionol bischloroformate (4.86g, 10.1 mmole) in methylene chloride (25 ml) was then added with stirring over 7 min. The mixture was stirred for a total of 45 min during which time a white precipitate formed. The mixture was then poured into 250 ml of rapidly stirred methanol and the suspended precipitate filtered, washed with water and methanol, and dried for 24 hr at 20 mm. Bithionol polycarbonate was obtained in 44% yield

(3.33g); inherent viscosity: 0.16 dl/g (0.5% in DMAc). The infrared and ^{1}H NMR spectra were identical to those described in Procedure III.

- Procedure II. A 150 ml round-bottomed flask was charged with bithionol (3.56g, 10.0 mmole), bithionol bischloroformate (4.86g, 10.1 mmole), and methylene chloride (90 ml) and cooled to 5°C. Pyridine (2.37g, 30.0 mmole) in methylene chloride (20 ml) was added over a period of 60 min. The reaction mixture turned pale pink in color with the addition of pyridine, but the color eventually disappeared as a while precipitate formed. The mixture was stirred for 16 hr, then poured into 600 ml of methanol. The white precipitate was filtered, washed with methanol and dried at 20 mm to yield 6.9g (90%) of bithionol polycarbonate with an inherent viscosity of 0.17 dl/g (0.5% in DMAc). The infrared and ^{1}H NMR spectra were identical to those described in Procedure III.

This procedure was repeated using DMAc as a solvent in place of methylene chloride; polymer yield: 18%; inherent viscosity: 0.17 dl/g (0.5% in DMAc). When collidine (3.67g, 30.0 mmole) was used in place of pyridine, again with methylene chloride as the solvent, the polymer yield was increased to 96% and the inherent viscosity to 0.20 dl/g (0.5% in DMAc).

- Procedure III. A glass polymerization tube was charged with bithionol bischloroformate (2.46g, 5.1 mmole)

and bithionol (1.76g, 5.0 mmole). The tube was warmed to 100°C in an oil bath over 1 hr while the pressure was lowered to 20 mm. The temperature was then increased to 200°C over 40 min and the mixture was held for an additional 1 hr at this temperature. During this period some gas bubbles were observed escaping from the molten reaction mixture. The pressure was further reduced to 0.05 mm and the temperature increased over 1 hr to 228°C, where it was held for 4.5 hr. After termination of the reaction, the resultant lightly colored polymer was dissolved in 50 ml of DMAc, precipitated into 500 ml of ethanol, filtered, washed with ethanol, and dried at 20 mm; yield bithionol polycarbonate: 3.20g (84%); inherent viscosity: 0.35 dl/g (0.5% in DMAc). The infrared spectrum (KBr) showed absorbtions at 3075 cm^{-1} (aromatic C-H stretching) and 1810 cm^{-1} (C=O stretching). See p. 222. The ^{1}H NMR spectrum (d_7-DMF) showed peaks at δ 7.0 and 7.3 (aromatic protons). See p. 208.

- Procedure IV. A 100 ml round-bottomed flask was charged with bithionol (53.41g, 150.0 mmole), diphenyl carbonate (33.73g, 157.5 mmole), and zinc oxide (0.08g, 1.0 mmole). The mixture was heated to 210°C while nitrogen was slowly bubbled through the molten reactants to facilitate removal of the phenol condensate. After most of the phenol had been removed (approximately 3.5 hr), the pressure was reduced to 20 mm over 1.5 hr. The temperature was then

raised to 235°C over 1 hr while the pressure was reduced to 3 mm where it was held for an additional 3 hr. At this point the molten polymer could be drawn into long thin fibers. When cooled, however, these fibers became extremely brittle and crumbled easily. The cooled glassy polymer was dissolved in DMAc (200 ml), precipitated into ethanol (1500 ml), filtered, washed with ethanol, and dried at 20 mm to yield 50.4g (88%) of an off-white polymer with an inherent viscosity of 0.46 dl/g (0.5% in DMAc). The infrared and ^{1}H NMR spectra were identical to those described in Procedure III. Differential scanning calorimetry studies indicated a glass transition temperature of 105°C for the polymer.

ANAL. calcd. for $C_{13}H_4Cl_4O_3S$: Cl, 37.12%. Found: Cl, 37.26%.

D. Bithionol alternating copolycarbonates.

1. Bithionol/ethylene glycol alternating copolycarbonate. A 150 ml round-bottomed flask was charged with bithionol bischloroformate (4.86g, 10.1 mmole), ethylene glycol (0.62g, 10.0 mmole), and methylene chloride (90 ml). A 12.2 ml aliquot of pyridine (2.37g, 30.0 mmole) in methylene chloride (15 ml) was added over a period of 70 min and the resulting mixture stirred for 24 hr. The clear solution was then poured into 400 ml of methanol and the resulting precipitate was filtered, washed with methanol

and dried at 20 mm. Yield of bithionol/ethylene glycol alternating copolycarbonate: 3.30g (70%); inherent viscosity: 0.16 dl/g (0.5% in DMAc). The infrared spectrum showed absorbtions at 2930 and 2850 cm^{-1} (C-H stretching) and 1770 cm^{-1} (C=O stretching). The ^{1}H NMR spectrum showed peaks at δ 4.2 ($C\underline{H}_2OCO$, 26) and 7.1-7.4 (aromatic protons, 28).

2. Bithionol/1,10-decanediol alternating copolycarbonate. Bithionol bischloroformate (4.86g, 10.1 mmole), 1,10-decanediol (1.75g, 10.0 mmole), and pyridine (2.37g, 30.0 mmole); light pink color upon addition of pyridine which disappeared after 50 min; polymer yield: 4.6g (79%); inherent viscosity: 0.22 dl/g (0.5% in DMAc); infrared spectrum: 2930 and 2850 cm^{-1} (C-H stretching) and 1770 cm^{-1} (C=O stretching). See p. 223. ^{1}H NMR: δ 1.1-2.0 (methylene protons, 60), 4.1-4.5 ($C\underline{H}_2OCO$, 12), and 7.1-7.6 (aromatic protons, 8). See p. 209.

ANAL calcd. for $C_{24}H_{24}Cl_4O_6S$: Cl, 24.35%. Found: Cl, 24.20%.

3. Bithionol/resorcinol alternating copolycarbonate. Bithionol bischloroformate (4.86g, 10.1 mmole), resorcinol (1.10g, 10.0 mmole), and pyridine (2.37g, 30.0 mmole); light yellow color accompanied by a fine precipitate upon addition of pyridine, both of which disappeared after 50 min; polymer yield: 3.7g (71%); inherent viscosity: 0.17 dl/g (0.5% in DMAc); infrared spectrum: 3075 cm^{-1} (aromatic

C-H stretching), 1785 cm^{-1} (C=O stretching), and 1205 cm^{-1} (C-O stretching). See p. 223. ^{1}H NMR: δ 7.0-7.6 (aromatic protons). See p. 209.

ANAL. calcd. for $C_{20}H_8Cl_4O_6S$: Cl, 27.37%. Found: Cl, 27.88%.

4. Bithionol/isopropylidenediphenol alternating copolycarbonate. Bithionol bischloroformate (4.86g, 10.1 mmole), isopropylidenediphenol (2.28g, 10.0 mmole), and pyridine (2.37g, 30.0 mmole); clear solution throughout reaction; polymer yield: 5.7g (90%); inherent viscosity: 0.21 dl/g (0.5% in DMAc); infrared spectrum: 3075 cm^{-1} (aromatic C-H stretching) and 1785 cm^{-1} (C=O stretching); ^{1}H NMR spectrum: δ 1.2 ($C\underline{H}_3$, 6H), 6.9-7.6 (aromatic protons, 12H).

5. Bithionol/4,4'thiobis(6-tert-butyl-o-cresol) alternating copolycarbonate. Bithionol bischloroformate (4.86g, 10.1 mmole), 4,4'-thiobis(6-tert-butyl-o-cresol) (3.58g, 10.0 mmole) and pyridine (2.37g, 30.0 mmole); light brown color upon addition of pyridine changing to red after 45 min; polymer yield: 5.5g (72%); inherent viscosity; 0.19 dl/g (0.5% in DMAc); infrared spectrum: 3075 cm^{-1} (aromatic C-H stretching), 2930 and 2860 cm^{-1} (C-H stretching), and 1785 cm^{-1} (C=O stretching); ^{1}H NMR: δ 1.1-1.6 ($(C\underline{H}_3)_3$, 30), 2.1 ($C\underline{H}_3$, 10), 7.0-7.5 (aromatic protons, 13).

E. Bithionol/polyethylene glycol alternating copolycarbonates.

1. Bithionol/ethylene glycol alternating copolycarbonates. A four inch test tube was charged with 5.10g (10.6 mmole) of bithionol bischloroformate and 0.66g (10.6 mmole) of ethylene glycol. The tube was then sealed with a two-holed rubber stopper and alternately evacuated and flushed with nitrogen a total of 5 times. Leaving a slow stream of nitrogen flowing, the tube was immersed in an oil bath at 108°C. The temperature decreased to 98°C as the contents of the tube melted (approximately 15 min) after which the temperature returned to 108°C. The contents were thoroughly mixed by bubbling nitrogen through the melt for 5 min. Bubbles of byproduct HCl could be seen escaping from the melt after approximately 20 min. The pressure was lowered to 20 mm after 1 hr at 108°C and left at this point for 12.5 hr after which the pressure was further lowered to 3 mm and the temperature increased to 180°C over a period of 4.5 hr. The viscous melt was cooled and formed 4.8g (96%) of a hard, glassy, slightly yellow polymer with an inherent viscosity of 0.43 dl/g (0.5% in DMAc). The infrared spectrum showed absorbtions at 2930 and 2850 cm^{-1} (C-H stretching) and 1770 cm^{-1} (C=O stretching). The ^{1}H NMR spectrum showed peaks at δ 4.2 ($C\underline{H}_2OCO$, 4H) and 7.2-7.4 (aromatic protons, 4H).

2. Bithionol/tetraethylene glycol alternating copolycarbonate. Bithionol bischloroformate (4.99g, 10.4 mmole) and tetraethylene glycol (2.02g, 10.4 mmole); yield 6.2g (99%) of a hard glassy polymer; inherent viscosity: 0.79 dl/g (0.5% in DMAc); infrared spectrum: 2940 and 2890 cm^{-1} (C-H stretching), 1770 cm^{-1} (C=O stretching), and 1100 cm^{-1} (C-O stretching); ^{1}H NMR: δ 3.4-3.8 ($C\underline{H}_2C\underline{H}_2O$, 16), 4.2 ($C\underline{H}_2OCO$, 6) and 7.2-7.6 (aromatic protons, 6).

3. Bithionol/PEG 400 alternating copolycarbonate. Bithionol bischloroformate (5.09g, 10.6 mmole) and Carbowax PEG 400 (4.22g, 10.6 mmole) in a six inch test tube; yield: 7.9g (93%) of a leathery polymer; inherent viscosity: 0.64 dl/g (0.5% in DMAc); infrared spectrum: 2890 cm^{-1} (C-H stretching), 1770 cm^{-1} (C=O stretching), and 1115 cm^{-1} (C-O stretching); ^{1}H NMR: δ 3.4-3.7 ($C\underline{H}_2C\underline{H}_2O$, 31), 4.2 ($C\underline{H}_2OCO$, 5), and 7.2-7.4 (aromatic protons, 4).

4. Bithionol/PEG 600 alternating copolycarbonate. Bithionol bischloroformate (4.99g, 10.4 mmole) and Carbowax PEG 600 (6.23g, 10.4 mmole) in a six inch test tube; yield: 10.1g (97%) of tacky polymer; inherent viscosity: 0.81 dl/g (0.5% in DMAc); infrared spectrum: 2890 cm^{-1} (C-H stretching), 1770 cm^{-1} (C=O stretching), and 1110 cm^{-1} (C-O stretching); ^{1}H NMR: δ 3.4-3.7 ($C\underline{H}_2C\underline{H}_2O$, 12), 4.2 ($C\underline{H}_2OCO$, 2), and 7.2-7.4 (aromatic protons, 1).

5. Bithionol/PEG 1000 alternating copolycarbonate. Bithionol bischloroformate (5.19g, 10.8 mmole) and Carbo-

wax PEG 1000 (10.79g, 10.8 mmole) in an eight inch test tube; yield: 14.1g (93%) of tacky polymer; inherent viscosity: 0.85 dl/g (0.5% in DMAc); infrared spectrum: 2895 cm^{-1} (C-H stretching), 1770 cm^{-1} (C=O stretching), and 1110 cm^{-1} (C-O stretching); ^{1}H NMR: δ 3.4-3.5 ($C\underline{H}_2C\underline{H}_2O$, 45) and 7.2 (aromatic protons, 2).

6. Bithionol/PEG 4000 alternating copolycarbonate. Bithionol bischloroformate (4.83g, 10.0 mmole) and Carbowax PEG 4000 (33.56g, 10.0 mmole) in an eight inch test tube; yield 32.4g (86%) of waxy polymer; inherent viscosity: 1.22 dl/g (0.5% in DMAc); infrared spectrum: 2890 cm^{-1} (C-H stretching), 1770 cm^{-1} (C=O stretching), and 1110 cm^{-1} (C-O stretching). See p. 222. ^{1}H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$). See p. 208.

ANAL. calcd. for $C_{160}H_{308}Cl_4O_{81}$: Cl, 3.86%. Found: Cl, 4.04%.

F. Bithionol terpolycarbonates containing PEG 4000.

1. Bithionol/ethylene glycol/PEG 4000 terpolycarbonate. An eight inch test tube was charged with 25.00g (7.5 mmole) of Carbowax PEG 4000, 0.69g (11.1 mmole) of ethylene glycol, and 9.19g (19.1 mmole) of bithionol bischloroformate. The tube was then sealed with a two-holed rubber stopper and alternately evacuated and flushed with nitrogen a total of 5 times. The tube was then lowered into a 105°C oil bath. The contents melted rapidly, and

were thoroughly mixed by bubbling nitrogen through the melt for 5 min. After 6.5 hr at 105°C the oil bath was heated to 194°C over a period of 2.5 hr. The pressure was lowered to 20 mm, where it was kept for 12 hr, after which it was lowered again to 3 mm and kept for 3 hr. The lightly colored polymer was a waxy substance that completely dissolved in water. Yield: 32.1g (97%); inherent viscosity: 0.44 dl/g (0.5% in DMAc); infrared spectrum: 2870 cm^{-1} (C-H stretching), 1775 cm^{-1} (C=O stretching, and 1115 cm^{-1} (C-O stretching). The ^{1}H NMR spectrum showed a peak at δ 3.4 ($C\underline{H}_2C\underline{H}_2O$).

2. Bithionol/1,3-propanediol/PEG 4000 terpolycarbonate. Carbowax PEG 4000 (25.02g, 7.5 mmole), 1,3-propanediol (0.63g, 8.3 mmole), and bithionol bischloroformate (7.80g, 16.2 mmole); polymer yield: 30.9g (86%); inherent viscosity: 0.53 dl/g (0.5% in DMAc); infrared spectrum: 2890 cm^{-1} (C-H stretching), 1775 cm^{-1} (C=O stretching), and 1115 cm^{-1} (C-O stretching); ^{1}H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$).

3. Bithionol/1,4-butanediol/PEG 4000 terpolycarbonate. Carbowax PEG 4000 (24.98g, 7.5 mmole), 1,4-butanediol (0.62g, 6.9 mmole), and bithionol bischloroformate (7.11g, 14.8 mmole); polymer yield: 30.2g (96%); inherent viscosity: 0.76 dl/g (0.5% in DMAc); infrared spectrum: 2880 cm^{-1} (C-H stretching), 1775 cm^{-1} (C=O stretching), and 1110 cm^{-1} (C-O stretching); ^{1}H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$).

4. Bithionol/1,6-hexanediol/PEG 4000 terpolycarbonate. Carbowax PEG 4000 (25.03g, 7.5 mmole), 1,6-hexanediol (0.78g, 6.6 mmole), and bithionol bischloroformate (6.96g, 14.5 mmole); polymer yield: 31.0g (98%); inherent viscosity: 0.78 dl/g (0.5% in DMAc); infrared spectrum: 2880 cm^{-1} (C-H stretching), 1770 cm^{-1} (C=O stretching), and 1115 cm^{-1} (C-O stretching); ^{1}H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$).

5. Bithionol/1,10-decanediol/PEG 4000 terpolycarbonate. Carbowax PEG 4000 (25.03g, 7.5 mmole), 1,10-decanediol (1.29g, 7.4 mmole), and bithionol bischloroformate (7.36g, 15.3 mmole); polymer yield = 31.6g (98%); inherent viscosity: 0.96 dl/g (0.5% in DMAc); infrared spectrum: 2880 cm^{-1} (C-H stretching), 1770 cm^{-1} (C=O stretching), and 1115 cm^{-1} (C-O stretching). See p. 224. ^{1}H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$). See p. 210.

The chlorine content of the polymer (8.10%) indicated a ratio of 7 1,10-decanediol segments to 93 PEG 4000 segments.

6. Bithionol/resorcinol/PEG 4000 terpolycarbonate. Carbowax PEG 4000 (25.11g, 7.5 mmole), resorcinol (0.82g, 7.5 mmole), and bithionol bischloroformate (7.42g, 15.4 mmole); 205°C for 9 hr at 760 mm, 205°C for 12 hr at 20 mm, 205°C for 3 hr at 3 mm; polymer yield: 30.1g (94%); inherent viscosity: 0.48 dl/g (0.5% in DMAc); infrared spectrum: 2875 cm^{-1} (C-H stretching), 1775 cm^{-1} (C=O stretch-

ing), and 1120 cm^{-1} (C-O stretching). See p. 224. ^1H NMR spectrum: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$). See p. 210.

The chlorine content of the polymer (19.43%) indicated a ratio of 7 resorcinol segments to 3 PEG 4000 segments.

7. Bithionol/hydroquinone/PEG 4000 terpolycarbonate. Carbowax PEG 4000 (24.99g, 7.5 mmole), hydroquinone (0.82g, 7.4 mmole), and bithionol bischloroformate (7.37g, 15.3 mmole); 205°C for 9 hr at 760 mm, 205°C for 12 hr at 20 mm, 205°C for 3 hr at 3 mm; polymer yield: 30.0g (94%); inherent viscosity: 0.41 dl/g (0.5% in DMAc); infrared spectrum: 2875 cm^{-1} (C-H stretching), 1775 cm^{-1} (C=O stretching), and 1120 cm^{-1} (C-O stretching); ^1H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$).

8. Bithionol/isopropylidenediphenol/PEG 4000 terpolycarbonate. Carbowax PEG 4000 (25.01g, 7.47 mmole), isopropylidenediphenol (1.71g, 7.5 mmole), and bithionol bischloroformate (7.42g, 15.4 mmole); 205°C for 9 hr at 760 mm, 205°C for 12 hr at 20 mm, 205°C for 3 hr at 3 mm; polymer yield: 30.9g (94%); inherent viscosity: 0.51 dl/g (0.5% in DMAc); infrared spectrum: 2880 cm^{-1} (C-H stretching), 1775 cm^{-1} (C=O stretching), and 1115 cm^{-1} (C-O stretching); ^1H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$).

9. Bithionol/4,4'-thiobis(6-tert-butyl-o-cresol)/PEG 4000 terpolycarbonate. Carbowax PEG 4000 (25.08g, 7.5 mmole), 4,4'-thiobis(6-tert-butyl-o-cresol) (2.69g, 7.5

mmole), and bithionol bischloroformate (7.43g, 15.4 mmole); 205°C for 9 hr at 760 mm, 205°C for 12 hr at 20 mm, 205°C for 3 hr at 3 mm; polymer yield: 30.4g (90%); inherent viscosity: 0.55 dl/g (0.5% in DMAc); infrared spectrum: 2880 cm^{-1} (C-H stretching), 1775 cm^{-1} (C=O stretching), and 1110 cm^{-1} (C-O stretching); ^{1}H NMR: δ 1.3 ($(CH_3)_3$, 2) and 3.4 ($C\underline{H}_2C\underline{H}_2O$, 5.8).

10. Bithionol/PEG 4000 copolycarbonate. Carbowax PEG 4000 (25.04g, 7.5 mmole), bithionol (2.68g, 7.5 mmole), and bithionol bischloroformate (7.42g, 15.4 mmole); 205°C for 9 hr at 760 mm, 205°C for 12 hr at 20 mm, 205°C for 3 hr at 3 mm; polymer yield: 30.0g (89%); inherent viscosity: 0.49 dl/g (0.5% in DMAc); infrared spectrum: 2885 cm^{-1} (C-H stretching), 1775 cm^{-1} (C=O stretching), and 1110 cm^{-1} (C-O stretching); ^{1}H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$).

G. Bithionol alternating copolyurethanes.

1. Bithionol/ethylenediamine alternating copolyurethanes. A 150 ml round-bottomed flask was charged with ethylenediamine (1.21g, 20.1 mmole) and methylene chloride (35 ml). Bithionol bischloroformate (4.89g, 10.2 mmole) in methylene chloride (20 ml) was added dropwise over 12 min. A white precipitate formed almost immediately. The mixture was then heated and stirred at reflux for an additional 1 hr. The cooled mixture was then left at room temperature for 24 hr after which it was poured into 500 ml

of methanol to yield a white precipitate which was filtered, washed with methanol, water, and methanol again, and dried at 20 mm. The yield of bithionol/ethylenediamine alternating copolyurethane was 2.4g (51%) and the inherent viscosity was 0.17 dl/g (0.5% in DMAc). The infrared spectra showed absorbtions at 3420 and 3340 cm^{-1} (amide N-H stretching), 2920 cm^{-1} (C-H stretching), and 1735 cm^{-1} (C=O stretching).

2. Bithionol/1,10-decanediamine alternating copolyurethane. 1,10-Decanediamine (3.45g, 20.0 mmole) and bithionol bischloroformate (4.86g, 10.1 mmole); polymer yield: 5.8g (100%); inherent viscosity: 0.21 dl/g (0.5% in DNAc); infrared spectrum: 3430-3320 cm^{-1} (amide N-H stretching), 2920 and 2850 cm^{-1} (C-H stretching), and 1735 cm^{-1} (C=O stretching). See p. 225. ^1H NMR: δ 1.0-1.7 (internal methylene protons, 28), 3.0-3.4 ($C\underline{H}_2N\underline{H}CO$, 9), and 7.2-7.8 (aromatic protons, 7). See p. 211.

ANAL. calcd. for $C_{24}H_{26}Cl_4N_2O_4S$: Cl, 24.43%. Found: Cl, 24.24%.

3. Bithionol/m-phenylenediamine alternating copolyurethane. m-Phenylenediamine (2.16g, 20.0 mmole) and bithionol bischloroformate (4.85g, 10.1 mmole); polymer yield: 1.6g (31%); inherent viscosity: 0.27 dl/g (0.5% in DMAc); infrared spectrum: 3420-3300 cm^{-1} (amide N-H stretching), 3075 cm^{-1} (aromatic C-H stretching), and 1760 cm^{-1} (C=O stretching). See p. 225. ^1H NMR: δ 6.9-7.5

(bithionol aromatic protons and CONH, 19) and 7.5-8.0 (m-phenylenediamine aromatic protons, 12). See p. 211.

ANAL. calcd. for $C_{20}H_{10}Cl_4N_2O_4S$: Cl, 27.47%. Found: Cl, 27.74%.

4. Bithionol/methylenedianiline alternating co-polyurethane - Procedure I. Methylenedianiline (3.94g, 19.9 mmole), and bithionol bischloroformate (4.83g, 10.0 mmole); polymer yield: 6.1g (100%); inherent viscosity: 0.24 dl/g (0.5% in DMAc); infrared spectrum: 3420-3320 cm^{-1} (amide N-H stretching), 3075 cm^{-1} (aromatic C-H stretching), and 1755 cm^{-1} (C=O stretching); ^1H NMR: δ 4.1 (ϕ-C$\underline{H}_2$-ϕ, 6), 6.9-7.5 (bithionol aromatic protons and CONH, 20), and 7.5-8.0 (methylenedianiline aromatic protons, 24).

- Procedure II. A 25 ml round-bottomed flask was charged with 4.29g (17.2 mmole) of methylenediisocyanate and 10 ml of dimethylacetamide. To this solution was added 6.11g (17.2 mmole) of bithionol in one portion. The contents were stirred for 20 min, then the flask was lowered into a 115°C oil bath for 2 hr. The resulting viscous solution was cooled, diluted to 30 ml with DMAc, and poured into 300 ml of water to give 9.76g (94%) of a light yellow solid. The inherent viscosity was 0.06 dl/g (0.5% in DMAc). The infrared and ^1H NMR spectra were identical to those described in Procedure I.

H. Bithionol copolyurethanes containing PEG 4000.

1. Bithionol/ethylenediamine copolyurethane containing PEG 4000. A 150 ml round-bottomed flask was charged with ethylenediamine (0.49g, 8.1 mmole), calcium hydroxide (5.56g, 75.0 mmole), Carbowax PEG 4000 (25.11g, 7.5 mmole), and toluene (90 ml). The mixture was heated to reflux and bithionol bischloroformate (7.74g, 16.1 mmole) in toluene (25 ml) was added over 5 min. The rapid initial reaction subsided within a few minutes and the mixture was stirred at reflux for a total of 5 hr. The viscous reaction mixture was then cooled and left at room temperature for 14 hr. The contents of the flask containing a swollen white precipitate were poured into 800 ml of 50% methanol containing 15 ml of concentrated HCl. The resulting suspension was centrifuged to separate the fine white polymer which was then washed with water and acetone and dried at 20 mm. The yield of the water swellable copolyurethane was 11.4g (36%) and the inherent viscosity was 0.31 dl/g (0.5% in DMAc). The infrared spectrum showed absorbtions at 3390 and 3340 cm^{-1} (amide N-H stretching), 2925 and 2850 cm^{-1} (C-H stretching), and 1780 cm^{-1} (C=O stretching). The ^{1}H NMR spectrum showed a peak at δ 3.4 ($C\underline{H}_2C\underline{H}_2O$).

2. Bithionol/1,3-propanediamine copolyurethane containing PEG 4000. 1,3-Propanediamine (0.61g, 8.3 mmole), calcium hydroxide (5.56g, 75.0 mmole), Carbowax PEG 4000

(25.07g, 7.5 mmole), and bithionol bischloroformate (7.81g, 16.2 mmole); polymer yield: 13.2g (41%); inherent viscosity: 0.30 dl/g (0.5% in DMAc); infrared spectrum: 3390 and 3340 cm^{-1} (amide N-H stretching), 2920 and 2860 cm^{-1} (C-H stretching), and 1780 cm^{-1} (C=O stretching); ^{1}H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$).

3. Bithionol/1,4-butanediamine copolyurethane containing PEG 4000. 1,4-Butanediamine (0.68g, 7.7 mmole), calcium hydroxide (5.56g, 75.0 mmole), Carbowax PEG 4000 (25.02g, 7.5 mmole), and bithionol bischloroformate (7.50g, 15.6 mmole); polymer yield: 17.7g (56%); inherent viscosity: 0.39 dl/g (0.5% in DMAc); infrared spectrum: 3390 and 3340 cm^{-1} (amide N-H stretching), 2920 and 2860 cm^{-1} (C-H stretching), and 1780 cm^{-1} (C=O stretching), ^{1}H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$).

4. Bithionol/1,6-hexanediamine copolyurethane containing PEG 4000. 1,6-Hexanediamine (1.04g, 8.9 mmole), calcium hydroxide (5.56g, 75.0 mmole), Carbowax PEG 4000 (25.10g, 7.5 mmole), and bithionol bischloroformate (8.12g, 16.9 mmole); polymer yield: 26.6g (81%); inherent viscosity: 0.60 dl/g (0.5% in DMAc); infrared spectrum: 3400 and 3350 cm^{-1} (amide N-H stretching), 2920 and 2860 cm^{-1} (C-H stretching), and 1780 cm^{-1} (1795 cm^{-1} shoulder) (C=O stretching); ^{1}H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$).

5. Bithionol/1,10-decanediamine copolyurethane containing PEG 4000. 1,10-Decanediamine (1.29g, 7.5 mmole),

calcium hydroxide (5.56g, 75.0 mmole), Carbowax PEG 4000 (25.10g, 7.5 mmole), and bithionol bischloroformate (7.43g, 15.4 mmole); polymer yield: 30.1g (93%); inherent viscosity: 0.64 dl/g (0.5% in DMAc); infrared spectrum: 3400 and 3350 cm^{-1} (amide N-H stretching), 2925 and 2850 cm^{-1} (C-H stretching), and 1795 and 1780 cm^{-1} (C=O stretching). See p. 226. ^{1}H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$). See p. 212.

The chlorine content (22.86%) of the polymer indicated a ratio of 78 1,10-decanediamine segments to 22 PEG 4000 segments.

6. Bithionol/m-phenylenediamine copolyurethane containing PEG 4000. m-Phenylenediamine (0.82g, 7.6 mmole), calcium hydroxide (5.56g, 75.0 mmole), Carbowax PEG 4000 (25.07g, 7.5 mmole), and bithionol bischloroformate (7.46g, 15.5 mmole); polymer yield: 15.3g (48%); inherent viscosity: 0.57 dl/g (0.5% in DMAc); infrared spectrum: 3400 and 3340 cm^{-1} (amide N-H stretching), 2940-2860 cm^{-1} (C-H stretching), and 1780 cm^{-1} (1800 cm^{-1} shoulder) (C=O stretching). See p. 226. ^{1}H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$). See p. 212.

The chlorine content of the polymer (21.66%) indicated a ratio of 75 m-phenylenediamine segments to 25 PEG 4000 segments.

7. Bithionol/p-phenylenediamine copolyurethane containing PEG 4000. p-Phenylenediamine (0.83g, 7.7 mmole), calcium hydroxide (5.56g, 75.0 mmole), Carbowax PEG 4000 (25.05g, 7.5 mmole), and bithionol bischloroformate (7.51g,

15.6 mmole); polymer yield: 13.8g (43%); inherent viscosity: 0.44 dl/g (0.5% in DMAc); infrared spectrum: 3400 and 3340 cm^{-1} (amide N-H stretching), 2940-2860 cm^{-1} (C-H stretching), and 1780 cm^{-1} (C=O stretching); ^{1}H NMR δ 3.4 ($C\underline{H}_2C\underline{H}_2O$).

8. Bithionol/methylenedianiline copolyurethane containing PEG 4000. Methylenedianiline (1.50g, 7.6 mmole), calcium hydroxide (5.56g, 75.0 mmole), Carbowax PEG 4000 (25.03g, 7.5 mmole), and bithionol bischloroformate (7.45g, 15.5 mmole); polymer yield: 19.5g (60%); inherent viscosity: 0.61 dl/g (0.5% in DMAc); infrared spectrum: 3410-3340 cm^{-1} (amide N-H stretching), 2930 and 2870 cm^{-1} (C-H stretching), and 1780 cm^{-1} (C=O stretching); ^{1}H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$).

9. Bithionol/piperazine copolyurethane containing PEG 4000. Piperazine (0.66g, 7.6 mmole), calcium hydroxide (5.56g, 75.0 mmole), Carbowax PEG 4000 (25.07g, 7.5 mmole), and bithionol bischloroformate (7.45g, 15.5 mmole); polymer yield: 13.3g (42%); inherent viscosity: 0.40 dl/g (0.5% in DMAc); infrared spectrum: 2925-2850 cm^{-1} (C-H stretching), and 1800 and 1780 cm^{-1} (C=O stretching); ^{1}H NMR: δ 3.4 ($C\underline{H}_2C\underline{H}_2O$).

I. Bithionol polyesters.

1. Poly(bithionol sebacate) - Procedure I. A 25 ml round-bottomed flask was charged with bithionol (1.83g, 5.2 mmole), tributylamine (2.02g, 10.9 mmole), and chloroform

(10 ml) to give a clear yellow solution. Sebacyl chloride (1.23g, 5.2 mmole) in chloroform (5 ml) was added in one portion. The reaction mixture became warm and a precipitate began forming. After 14 hr the mixture was poured into 250 ml of methanol. The resulting fluffy white precipitate was filtered, washed with methanol, and dried at 20 mm. The yield of polymer was 2.29g (85%) and the inherent viscosity was 0.18 dl/g (0.5% in DMAc). The infrared and ^{1}H NMR spectra were identical to those described in Procedure II.

- Procedure II. A six inch test tube was charged with 3.56g (10.0 mmole) of bithionol and 2.31g (10.0 mmole) of dimethylsebacate. The tube was alternately evacuated and flushed with nitrogen a total of 4 times. Leaving nitrogen flowing slowly through the tube, the contents were heated to 205°C over 105 min where they were left for 4.5 hr. The pressure was then lowered to 20 mm, then 12 hr later to 3 mm. After 3 more hr the viscous, slightly colored polymer was cooled to a hard glass, dissolved in 40 ml of methylene chloride, and precipitated into 350 ml of methanol to give 4.9g (94%) of a white powder with an inherent viscosity of 0.56 dl/g (0.5% in DMAc). The infrared spectrum showed absorbtions at 2930 and 2850 cm^{-1} (C-H stretching), and 1775 cm^{-1} (C=O stretching). See p. 227. The ^{1}H NMR spectrum showed peaks at δ 1.3 (internal $C\underline{H}_2$, 8H), 1.7 ($C\underline{H}_2CH_2COO$, 4H), 2.6 ($C\underline{H}_2COO$, 4H), and 7.1-7.6

(aromatic protons, 4H). See p. 213.

ANAL. calcd. for $C_{22}H_{20}Cl_4O_4S$: Cl, 27.15%. Found: Cl, 27.41%.

2. Poly(bithionol isophthalate) - Procedure I. Bithionol (3.57g, 10.0 mmole), tributylamine (3.89g, 21.0 mmole), and isophthaloyl chloride (2.04g, 10.0 mmole); yield: 4.70g (97%) of white polymer; inherent viscosity: 0.02 dl/g (0.5% in $CHCl_3$). This procedure was repeated using DMAc in place of chloroform to give 4.52g (93%). of polymer; inherent viscosity: 0.06 dl/g (0.5% in $CHCl_3$). The infrared and ^1H NMR spectra were identical to those described in Procedure IV.

- Procedure II. Bithionol (3.56g, 10.0 mmole), tetrabutylammonium bromide (0.20g, 0.6 mmole), and sulfolane (15 ml) were charged into a 50 ml round-bottom flask. The contents were heated to 185°C to give a clear, light yellow solution. Isophthaloyl chloride (2.03g, 10.0 mmole) in sulfolane (10 ml) was then added over 30 min while nitrogen was continuously bubbled through the solution. After 24 hr the thick reaction mixture, containing a large amount of colored precipitate, was cooled and poured into 300 ml of methanol to give 4.59g (94%) of an insoluble beige polymer. The infrared and ^1H NMR spectra were identical to those described in Procedure IV.

- Procedure III. A one quart Waring blender was charged with bithionol (3.56g, 10.0 mmole), sodium

hydroxide (0.81g, 20.0 mmole), tetrabutylammonium bromide (0.66g, 2.1 mmole), sodium dodecyl sulfate (1.00g, 3.5 mmole), water (110 ml), and chloroform (10 ml). To the rapidly stirred solution was added 2.03g (10.0 mmole) of isophthaloyl chloride in 20 ml of chloroform. After stirring for 20 min the emulsion was broken by adding 200 ml of methanol. The resulting precipitate was filtered, washed with water and methanol and dried at 20 mm. The yield of polymer was 4.87g (100%) and the inherent viscosity was 0.07 dl/g (0.5% in DMAc). The infrared and ^{1}H NMR spectra were identical to those described in Procedure IV.

- Procedure IV. A six inch test tube was charged with 3.56g (10.0 mmole) of bithionol and 1.94g (10.0 mmole) of dimethylisophthalate. After alternately evacuating and flushing with nitrogen 4 times, the contents were heated to 205°C over 105 min. With nitrogen bubbling through the reaction melt the mixture was left at 205°C for 4.5 hr, after which the pressure was lowered to 20 mm. After 12 hr the pressure was lowered again to 3 mm for an additional 3 hr. The resulting hard, glassy product was dissolved in 50 ml of DMAc and precipitated into 400 ml of methanol to give 4.9g (100%) of beige colored polymer with an inherent viscosity of 0.38 dl/g (0.5% in DMAc). The infrared spectrum showed absorbtions at 3070 cm^{-1} (aromatic C-H stretching), 1760 cm^{-1} (C=O stretching), and 1195 cm^{-1} (C-O

stretching). See p. 227. The ^{1}H NMR showed broad absorbtions at δ 7.0-8.3 (aromatic protons). See p. 213.

ANAL. calcd. for $C_{30}H_8Cl_4O_4S$: Cl, 29.17%. Found: 29.70%.

J. Bithionol polymers containing phosphorous.

1. Poly(bithionol phenylphosphate). A six inch test tube was charged with 7.95g (22.34 mmole) of bithionol and 4.71g (22.34 mmole) of phenyldichlorophosphate. After alternately evacuating and flushing the tube with nitrogen 5 times, the tube was lowered into an oil bath at 205°C. When the contents had melted nitrogen was bubbled through the melt to ensure mixing. The mixture gradually became more viscous. After 6 hr the pressure was lowered to 20 mm where it was held for an additional 12 hr. The temperature was then raised to 235°C and the pressure lowered to 3 mm over 1 hr. After 6 hr the tube was removed from the oil bath and cooled. The hard, glassy product was dissolved in 30 ml of methylene chloride, filtered and poured into 200 ml of 80% methanol to give 8.4g (76%) of white powdery polymer with an inherent viscosity of 0.19 dl/g (0.5% in DMAc). The infrared spectrum showed absorbtions at 3070 (aromatic C-H stretching), 1435 cm^{-1} (aromatic C-C stretching), 1305 cm^{-1} (P=O stretching), and 1190 cm^{-1} (P-O stretching). See p. 230. The ^{1}H NMR showed absorbtions at δ 7.2-7.7 (aromatic protons). See p. 216.

ANAL. calcd. for $C_{18}H_9Cl_4O_4PS$: Cl, 28.70%. Found: Cl, 28.51%.

2. Poly(bithionol phenylphosphonate). Bithionol (7.45g, 20.9 mmole) and phenylphosphonic dichloride (4.07g, 20.9 mmole); yield: 5.7g (57%) of beige polymer; inherent viscosity: 0.08 dl/g (0.5% in DMAc); infrared spectrum: 3060 cm^{-1} (aromatic C-H stretching), 1430 cm^{-1} (aromatic C-C stretching), and 910 cm^{-1} (P-O stretching). See p. 230.

ANAL. calcd. for $C_{18}H_9Cl_4O_3PS$: Cl, 29.66%. Found: Cl, 29.21%.

3. Poly(bithionolphenylphosphinate). Bithionol (7.64g, 21.5 mmole), and dichlorophenylphosphine (3.84g, 21.5 mmole); yield: 1.9g (19%) of tacky orange polymer; inherent viscosity: 0.16 dl/g (0.5% in DMAc); infrared spectrum: 3400 and 3340 cm^{-1} (O-H stretching), 3070 cm^{-1} (aromatic C-H stretching), 1455 cm^{-1} (aromatic C-C stretching) and 1220 cm^{-1} (P-O stretching). See p. 231. ^1H NMR: δ 6.9 and 7.2 (bithionol aromatic protons, 19) and 7.4-8.0 (phosphinate aromatic protons, 26). See p. 216.

ANAL. calcd. for $C_{18}H_9Cl_4O_2PS$: Cl, 30.69%. Found: 34.10%.

V. Preparation of Hindered Bisphenol Polyesters

A. Poly[4,4'-methylenebis(6-tert-butyl-o-cresol)sebacate]. A 25 ml round-bottomed flask was charged with 1.70g (5.0

mmole) of 4,4'-methylenebis(6-tert-butyl-o-cresol), 1.86g (10.0 mmole) of tributylamine, and 5 ml of chloroform. To the clear solution was added 1.19g (5.0 mmole) of sebacyl chloride in 5 ml of chloroform in one portion. The mixture was stirred for 8 hr, then poured into 100 ml of methanol. The resulting yellow product was washed with methanol and dried for 48 hr at 0.1 mm. The yield of hard elastomer was 1.96g (77%) and its inherent viscosity was 0.24 dl/g (0.5% in $CHCl_3$). The infrared spectrum showed absorbtions at 2930 and 2850 cm^{-1} (C-H stretching) and 1755 cm^{-1} (C=O stretching). See p. 228. The ^1H NMR spectrum showed absorbtions at δ 1.3-1.8 (internal $C\underline{H}_2$ and $(C\underline{H}_3)_3$, 39), 2.1 ($C\underline{H}_3$, 6), 2.5-2.9 ($C\underline{H}_2COO$, 4), 3.9 (ϕ-$C\underline{H}_2$-ϕ, 2), and 6.9-7.2 (aromatic protons, 4). See p. 214.

ANAL. calcd. for $C_{33}H_{46}O_4$: C, 78.22%, H, 9.15%. Found: C, 76.61%, H, 9.80%.

B. Poly[2,2'-methylenebis(6-tert-butyl-p-cresol)sebacate].

2,2'-Methylenebis(6-tert-butyl-p-cresol) (1.69g, 5.0 mmole), tributylamine (1.86g, 10.0 mmole), and sebacyl chloride (1.19g, 5.0 mmole); yield of white elastomer: 1.67g (67%); inherent viscosity: 0.23 dl/g (0.5% in $CHCl_3$); infrared spectrum: 2930 and 2850 cm^{-1} (C-H stretching) and 1755 cm^{-1} (C=O stretching). See p. 228. ^1H NMR spectrum: δ 1.2-2.0 (internal $C\underline{H}_2$ and $(C\underline{H}_3)_3$, 31), 2.0-2.7 ($C\underline{H}_3$ and $C\underline{H}_2COO$, 12), 3.4-3.8 (ϕ-$C\underline{H}_2$-ϕ, 3) and 6.7-7.2 (aromatic protons, 4).

See p. 214.

ANAL. calcd. for $C_{33}H_{46}O_4$: C, 78.22%; H, 9.15%. Found: C, 76.43%; H, 9.55%.

C. Poly[4,4'-thiobis(6-tert-butyl-m-cresol)sebacate]. 4,4'-Thiobis(6-tert-butyl-m-cresol) (1.78g, 5.0 mmole), tributylamine (1.86g, 10.0 mmole), and sebacyl chloride (1.19g, 5.0 mmole); yield colorless, leathery polymer: 2.42g (93%); inherent viscosity: 0.59 dl/g (0.5% in $CHCl_3$); infrared spectrum: 2930 and 2860 cm^{-1} (C-H stretching) and 1755 cm^{-1} (C=O stretching). See p. 229. ^1H NMR spectrum: δ 1.1-2.0 (internal $C\underline{H}_2$ and $(C\underline{H}_3)_3$, 41), 2.1-2.8 ($C\underline{H}_3$ and CH_2COO, 16), and 6.8-7.4 (aromatic protons, 4). See p. 215.

ANAL. calcd. for $C_{32}H_{44}O_4S$: C, 73.24%; H, 8.45%; S, 6.11%. Found: C, 72.67%; H, 9.17%; S, 5.85%.

D. Poly[4,4'-thiobis(6-tert-butyl-o-cresol)sebacate]. 4,4'-Thiobis(6-tert-butyl-o-cresol) (1.79g, 5.0 mmole), tributylamine (1.86g, 10.0 mmole), and sebacyl chloride (1.19g, 5.0 mmole); yield light yellow, leathery polymer: 2.35g (90%); inherent viscosity: 0.65 dl/g (0.5% in $CHCl_3$); infrared spectrum: 2930 and 2850 cm^{-1} (C-H stretching) and 1755 cm^{-1} (C=O stretching). See p. 229. ^1H NMR spectrum: δ 1.1-2.2 (internal $C\underline{H}_2$, $(C\underline{H}_3)_3$, and CH_3, 51), 2.3-2.8 ($C\underline{H}_2COO$, 6), and 7.0-7.4 (aromatic protons, 5). See p. 215.

ANAL. calcd. for $C_{32}H_{44}O_4S$: C, 73.24%; H, 8.45%;

S, 6.11%. Found: C, 72.19%; H, 8.34%; S, 6.18%.

VI. Measurement of the Rates of Hydrolysis of Bithionol Polymers

A. Preparation of buffer solutions.

1. pH 4.0 buffer. Potassium biphthalate (2.55g, 12.5 mmole) was dissolved in water to make 250 ml.

2. pH 10.0 buffer. Sodium bicarbonate (0.86g, 10.3 mmole) and 0.1007 M aqueous sodium hydroxide (43.8 ml) were dissolved in water to make 250 ml.

3. pH 7.4 buffer. Monobasic potassium phosphate (4.73g, 34.8 mmole) and dibasic sodium phosphate (17.28g, 121.7 mmole) were dissolved in water to make 4000 ml.

B. Preparation of polymer solutions. Volumetric flasks (100 ml) were charged with powdered polymer and buffer solution and the resultant mixtures were stirred for 24 hr. The flasks were then brought to volume with additional buffer solution.

C. Determination of polymer concentrations. Duplicate 5 ml aliquots of each of the polymer solutions prepared above were pipetted into tared aluminum weighing pans. The pans were left in a forced air oven at 50-55°C until a constant weight was reached. After subtracting the weight due to the nonvolatile components of the buffer solutions the quantities listed in Table 7 were obtained.

TABLE 7

SOLUBILITY OF POLYMERS IN AQUEOUS SOLUTION[1]

Polymer	Solubility in g/100 ml
Bithionol polycarbonate	<0.01
Bithionol/1,10-decanediol alternating copolycarbonate	<0.01
Bithionol/resorcinol alternating copolycarbonate	<0.01
Bithionol/PEG 4000 alternating copolycarbonate	>3.00
Bithionol/1,10-decanediol/PEG 4000 terpolycarbonate	>3.00
Bithionol/resorcinol/PEG 4000 terpolycarbonate	<0.01
Bithionol/1,10-decanediamine alternating copolyurethane	<0.01
Bithionol/m-phenylenediamine alternating copolyurethane	<0.01
Bithionol/1,10-decanediamine copolyurethane with PEG 4000	<0.01
Bithionol/m-phenylenediamine copolyurethane with PEG 4000	<0.01
Poly(bithionol sebacate)	<0.01
Poly(bithionol isophthalate)	<0.01
Poly(bithionol phenylphosphate)	<0.01
Poly(bithionol phenylphosphonate)	<0.01
Poly(bithionol phenylphosphinate)	<0.01

[1] pH 7.4

D. Preparation of bithionol absorbtion calibration curve. Bithionol was charged into 100 ml volumetric flasks and dissolved in enough pH 10.0 buffer solution to bring the flasks to volume. A 1 ml aliquot from each of these solutions was then diluted with water to make 100 ml. The ultraviolet absorbtion of each of these solution was then measured at 318.0 nm using a 1 cm quartz cuvette.

E. Measurement of the rate of release of bithionol from polymer solutions. The aqueous polymer solutions prepared above were immersed in a constant temperature bath held at 37.0 ± 0.2°C. At periodic intervals aliquots were removed from each, diluted as necessary with buffer solution (pH 10.0), and the ultraviolet absorbance at 318.0 nm measured using a 1 cm quartz cuvette.

VII. Measurements

Infrared spectra were recorded on Perkin-Elmer Model 727 or Model 283 spectrophotometers. Solid samples were measured as KBr pellets and liquid samples were measured between NaCl plates. The infrared spectra of some of the polymer samples were measured as films cast directly onto a single NaCl plate from a dichloromethane solution. The peak assignments were made to the nearest 5 cm^{-1}.

The ^{1}H NMR spectra were recorded on a 60 MHz R-24 Hitachi Perkin-Elmer spectrometer. Solutions were generally

10 to 15% in deuterated chloroform, deuterated dimethyl sulfoxide, deuterated acetone, or deuterated dimethylformamide.

Ultraviolet spectra were recorded on a Beckman MVI spectrometer in a double-beam servo mode. The maximum absorbances and the corresponding wavelengths were determined by dialing in the wavelength and recording the absorbance value presented on the digital display.

The thermal properties of the polymers were examined on a Perkin-Elmer DSC-2 differential scanning calorimeter at a scanning rate of 20°C/min. The instrument was calibrated against an indium standard.

The melting points of low molecular weight compounds were measured on a MEL-TEMP capillary melting point apparatus and are uncorrected.

Microanalyses were done by the Microanalytical Laboratory, Office of Research Services, University of Massachusetts, Amherst, Massachusetts.

C H A P T E R I I I

RESULTS AND DISCUSSION

I. Objectives

The objective of this research was to synthesize several novel polymers containing active pharmaceutical agents as integral parts of the chain backbones and to determine some of the factors affecting the rate of release of these biologically active agents from the polymer systems. In order to do this, two drugs, primaquine (8-(4-amino-1-methylbutylamino)-6-methoxyquinoline), a potent antimalarial, and bithionol (2,2'-thiobis(4,6-dichlorophenol)), an effective bacteriostat, were condensed with a number of different difunctional compounds to form a variety of polyurethanes, polyureas, polyesters, and polycarbonates, as well as different polyesters of phosphorous, phosphonic, and phosphoric acids. The hydrolytic stabilities of the resultant polymers were then studied with an emphasis on determining the rate of release of active agents from the polymers under conditions resembling those encountered in a physiological environment. In order to eliminate ambiguity in interpreting the results, a simple aqueous environment was used in the

hydrolysis studies. It was felt that actual biological systems would not yield as much fundamental information about the hydrolytic susceptibility of the different polymers because of the inherent complexity of such environments. The aqueous environments used were maintained at a pH of 7.4 and at a temperature of 37°C.

The rate constants for the hydrolysis of representative water soluble polymers containing bithionol ranged from 3.5×10^{-2} to 1.7×10^{-1} liter·mole^{-1}·min^{-1} at pH 7.4 and up to 1.6 liter·mole^{-1}·min^{-1} at pH 10.0 based on second-order kinetics. Insoluble polymers, on the other hand, tended to degrade at rates less than 1.4×10^{-11} mole·min^{-1} based on zero-order kinetics.

II. Polymerization of Primaquine

A. Isolation of primaquine. Primaquine could be obtained commercially in high purity as the diphosphate salt. Since many of the reactions performed in this research required primaquine as the free amine, it had to be isolated from its salt as a pure compound. This was accomplished by making an aqueous solution of primaquine diphosphate basic with an excess of sodium carbonate. This was done with care, as the CO_2 produced caused the reaction mixture to foam. Free primaquine, being sparingly soluble in water, oiled out of the aqueous mixture as a viscous brown liquid. This could be extracted with one of several organic solvents,

however, chloroform or methylene chloride were used most often. The combined organic layers were then dried over calcium chloride, filtered, and concentrated under reduced pressure or by evaporation under nitrogen to yield a brown oil. This oil was then distilled under high vacuum (pressures less than 0.05 mm were usually necessary) to give a clear, colorless, liquid identifiable as pure primaquine. Care had to be taken when distilling the compound to prevent oxidation.

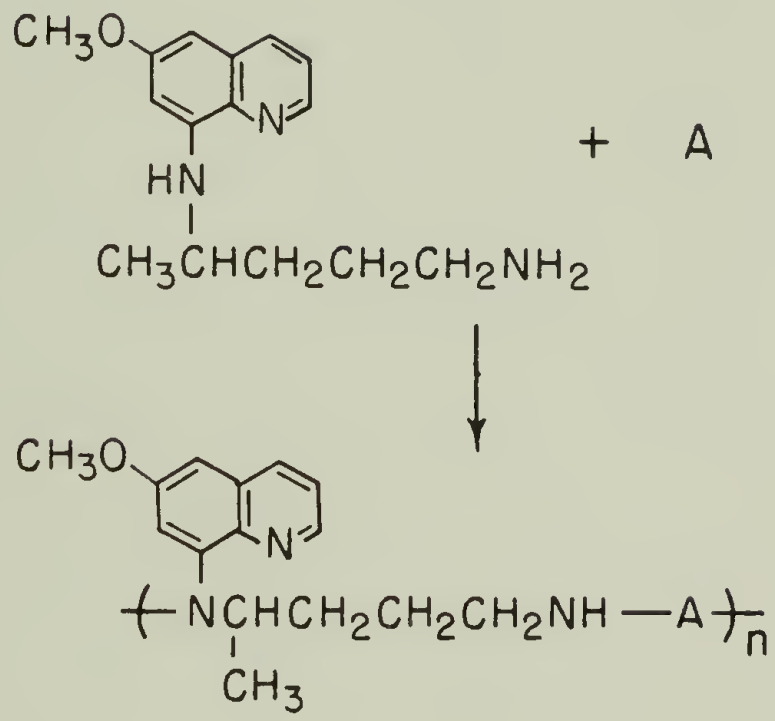
Both the infrared and ^{1}H NMR spectra of the compound were identical to those presented in the literature.[144]

B. Reaction of primaquine with difuctional intermediates using one-step polymerization techniques. Primaquine was allowed to react with difunctional intermediates in an attempt to incorporate the drug into a polymer chain through both the primary and secondary amino groups, as illustrated in Figure 7. Standard one-step polycondensation techniques were used.

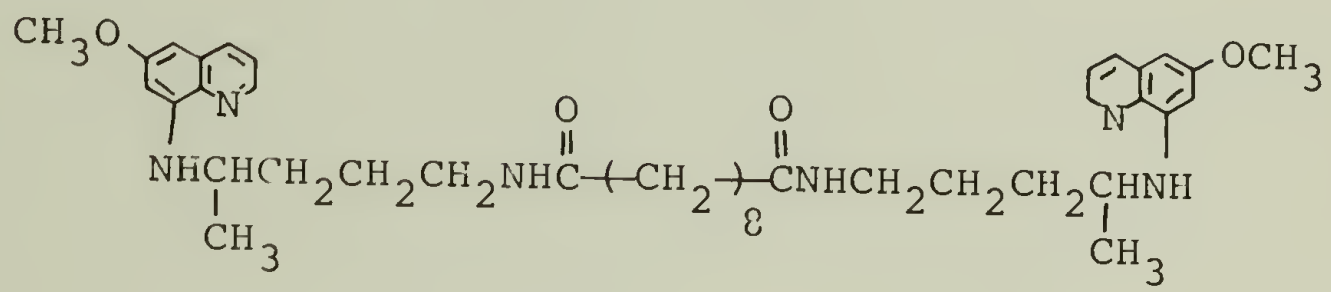
Equimolar portions of primaquine and sebacyl chloride were allowed to react in a chloroform solution with calcium hydroxide present as an acid acceptor. The product, a sticky yellow solid, showed absorbtions in the infrared corresponding to amide N-H stretching (3330-3360 cm^{-1} region), C=O stretching (1645 cm^{-1}, Amide I band), and N-H bending (1560 cm^{-1}, Amide II band), which indicated the

Figure 7. Polymerization of primaquine using a one-step polymerization scheme.

One-Step Polymerization Scheme



presence of an amide group. The formation of the disubstituted sebacamide (XII) was indicated by a microanalysis of the product which was found to contain 70.21% C, 8.29% H, and 12.08% N (ANAL. calcd. for $C_{40}H_{56}N_6O_4$: C, 70.14%; H, 8.24%; N, 12.27%).



XII

A product with an infrared spectrum identical to that described above was obtained when the same procedure was used at the temperature of refluxing chloroform.

A stirred interfacial polycondensation technique was then used in an attempt to produce high molecular weight polymer from primaquine and sebacyl chloride. Chloroform, sodium carbonate, and sodium dodecyl sulfate were used as the solvent, acid acceptor, and emulsifier, respectively. No precipitate was formed during the 30 min allowed for the reaction. A product with an infrared spectrum identical to that shown by the sebacamide obtained from the reactions performed in solution was isolated from the organic layer of the reaction mixture.

The reaction of primaquine with 1,6-diisocyanatohexane in chloroform solution was also examined. The reac-

tion was found to be relatively rapid, with the solution warming immediately upon mixing the reactants. After several hours, fine white crystals were found suspended in the yellow solution. The oil obtained after concentrating the filtered reaction mixture was of low molecular weight (as indicated by η_{inh}) and showed strong absorbtions in the infrared spectrum at 3430 and 3320 cm^{-1} and at 1620 and 1580 cm^{-1}, indicating the presence of N-H and C=O groups respectively. The insoluble crystals isolated from the reaction mixture, on the other hand, were found to show strong absorbtions in the infrared spectrum at 2270 cm^{-1}, and at 1640 and 1600 cm^{-1}, corresponding to isocyanate and carbonyl stretching respectively. An uncommon absorbtion at 810 cm^{-1} was also observed.

The formation of low molecular weight and insoluble products in these reactions demonstrated the difficulty of synthesizing polymers based on primaquine using standard one-step polycondensation procedures. This difficulty was attributed to the difference in reactivity between the two amino groups in question, one a primary aliphatic amine of relatively high reactivity, and one a sterically hindered secondary aromatic amine of greatly reduced reactivity. Although it was apparent that nearly quantitative substitution of the primary amine was taking place, the reaction involving the secondary amine did not appear to be proceeding to completion, thus preventing the preparation of high

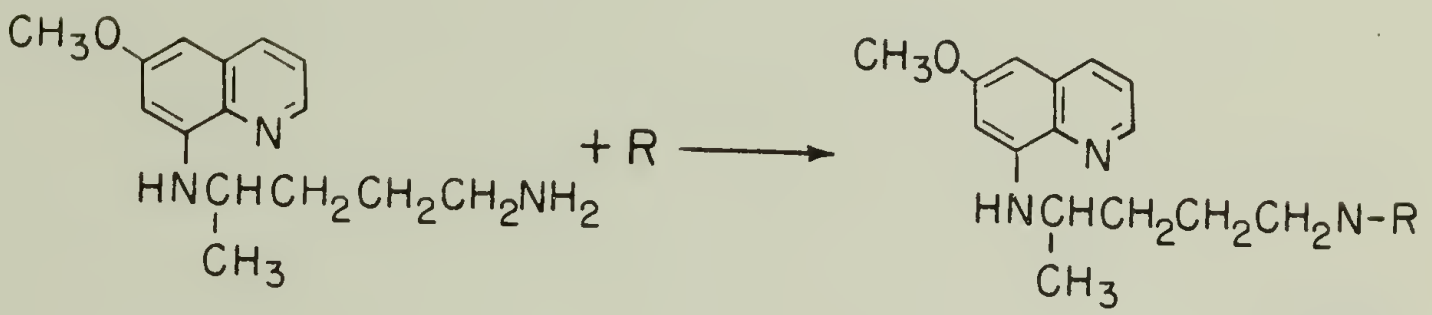
molecular weight polymers.

C. Attempted polymerization of primaquine using a multi-step polymerization scheme. Although the difference in reactivity between the primary and the secondary amine made a one-step polymerization of primaquine nearly impossible, it was thought that a multi-step procedure could be used to circumvent the problem. The reaction scheme illustrated in Figure 8 was considered as a means of doing so. The first step in the scheme involved the synthesis of a derivative of primaquine with the primary amine chemically blocked or "protected" against further reaction. This blocked primaquine derivative (XIII) could then be reacted in a two to one mole ratio with a reactive difunctional intermediate such as an acid chloride to form the "blocked dimer" intermediate (XIV). The primary amino groups could then be regenerated by selectively removing the blocking groups to form the "dimer" (XV) now possessing two primary aliphatic amines of equal reactivity. This compound could then be polymerized using conventional polycondensation techniques to produce polymers containing primaquine as integral parts of the chain backbones.

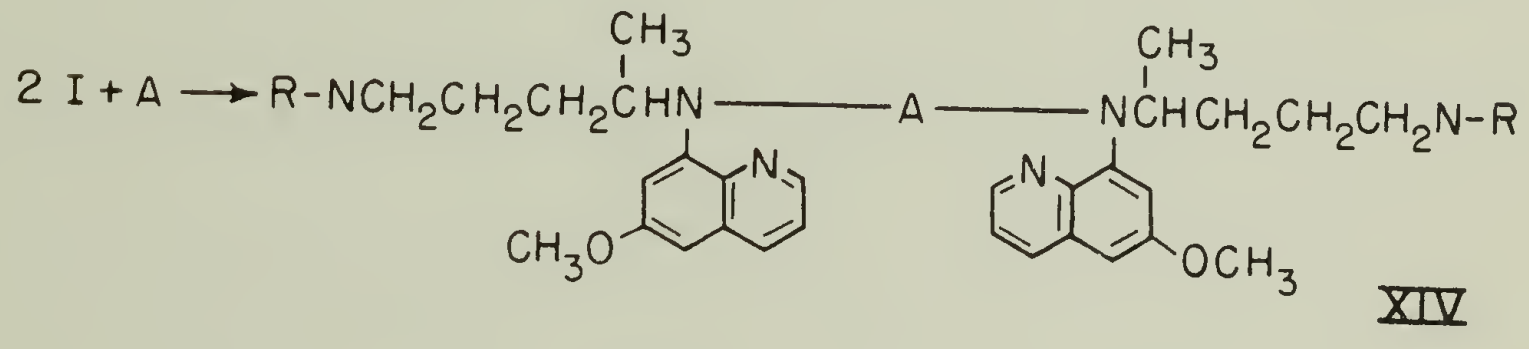
1. Preparation of phthalimido primaquine. The phthalimido derivative of primaquine was prepared in 69% yield from an equimolar mixture of primaquine and phthalic anhydride. Unreacted primaquine was removed from the reac-

Figure 8. Polymerization of primaquine using a multi-step polymerization scheme.

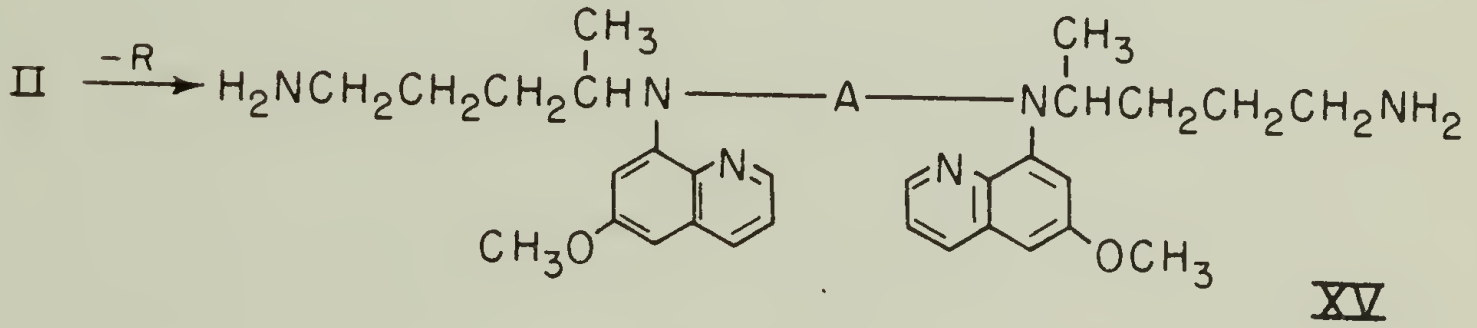
Multi-Step Polymerization Scheme



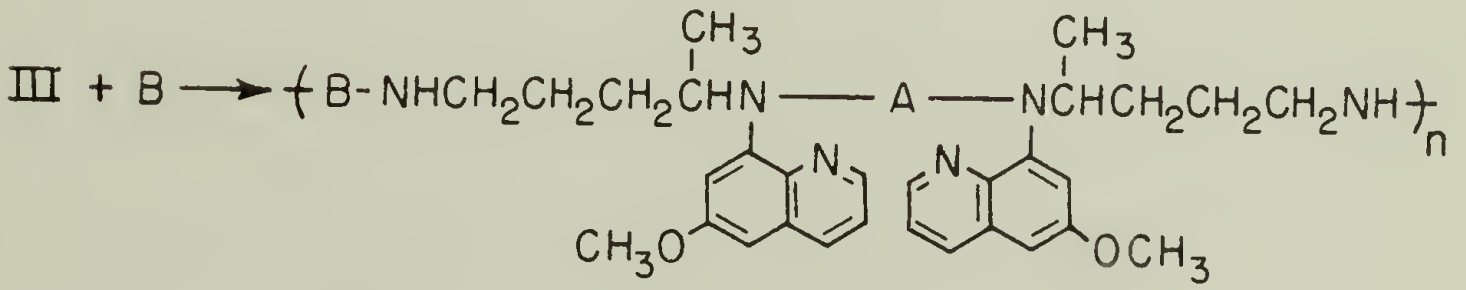
XIII



XIV



XV



R = Amine Blocking Group

A = Acid Chloride, etc.

B = Acid Chloride, etc.

tion solution with hot aqueous hydrobromic acid. Pure phthalimido primaquine was isolated from the crude material (a yellow oil) by recrystallizing from methanol. Care had to be taken during the recrystallization, however, as the material had a tendency to separate from the solvent as an oil instead of as a crystalline solid. This phenomenon is characteristic of primaquine derivatives, as many of them are difficult to purify by conventional techniques. In this case, a 2% methanol solution and temperatures less than 65°C had to be used to prevent the "oiling out" of the product. Very slow cooling and the use of seed crystals were also found useful. After several recrystallizations bright yellow crystals (mp 91-2°C, lit. mp[145] 89.0-90.5°C) were obtained.

The infrared spectrum was consistent with the expected structure showing a strong absorbtion due to the phthalimide carbonyl groups at 1710 cm^{-1}. The ^{1}H NMR spectrum, which showed overlapping multiplets in the aromatic region, was also consistent with this structure. The ratio of integrated peak areas showed the expected ratio of aromatic to aliphatic protons.

2. Reaction of phalimido primaquine with difunctional intermediates. The reactions of phthalimido primaquine with oxalyl chloride, succinyl chloride, sebacyl chloride, isophthaloyl chloride, 1,6-diisocyanatohexane (HMDI), 4,4'-diisocyanatodiphenylmethane (MDI), diethyl-

oxalate, phenoxybenzene-4,4'-disulfonyldichloride, and a trifluoroacetic/adipic mixed anhydride were investigated. Reactions with the four acid chlorides were performed using two different procedures and four different solvents. The first procedure involved the reaction at room temperature of phthalimido primaquine with the acid chlorides in a four to one molar ratio in the presence of calcium hydroxide as an acid acceptor. Methylene chloride, sulfolane, benzene, and acetonitrile were used as solvents. The second series of reactions was performed with collidine as an acid acceptor. In the second procedure, the reaction mixture was heated to 60°C after the addition of collidine and left for 8 hr. Benzene, sulfolane, and acetonitrile were used as solvents. As can be seen in Table 8, a reaction did occur in all cases, as indicated by rapid color changes and/or precipitate formation. Both infrared and thin layer chromatographic analysis of each of the reaction mixtures indicated that complicated mixtures of products were formed, however, no compounds with "blocked dimer" intermediate (XIV) structures were isolable in a pure state.

TABLE 8

APPEARANCE OF REACTION MIXTURES CONTAINING PHTHALIMIDO PRIMAQUINE AND ACID CHLORIDES

Solvent	Acid Chloride			
	Oxalyl	Succinyl	Sebacyl	Isophthaloyl
Benzene	yellow	green	orange	yellow
Methylene chloride	yellow	green	orange	yellow
Sulfolane	yellow, turning to orange	dark green, turning to black	orange	yellow
Acetonitrile	yellow, turning to orange	dark green, turning to black	orange	yellow

Reactions with the two isocyanates, HMDI and MDI, were performed in methylene chloride solution overnight. A dark yellow-brown color was observed in both reaction mixtures within a few minutes, accompanied by the formation of precipitates that were light in color. The soluble materials isolated from the reactions were found to be complex mixtures of reaction products, however, again no pure compounds could be isolated in a form suitable for proper characterization. The infrared spectra of the precipitated solids, on the other hand, showing absorbtions at 2270 cm^{-1}, almost uniquely characteristic of isocyanate groups, and at 1645 and 1600 cm^{-1}, attributed to carbonyl

stretching, indicated the formation of isocyanate trimerization products.

The reaction of phthalimido primaquine with diethyl oxalate in a 2 to 1 mole ratio was conducted overnight in DMF. A dark tarry residue suspended in a yellow-brown solution resulted. Thin layer chromatographic analysis showed the presence of predominantly unreacted starting material in the solution, while the residue was insoluble in most organic solvents. The infrared spectrum indicated the presence of both oxamide and oxalate, in addition to aromatic groups, however, no further identification was possible.

Phthalimido primaquine was also allowed to react with phenoxybenzene-4,4'-disulfonyldichloride. Although the reaction mixture gradually changed from a clear yellow color to a green which slowly darkened to an almost black, no identifiable products could be isolated in a pure state.

A mixed dianhydride of trifluoroacetic acid and adipic acid was prepared by reacting a six to one excess of trifluoroacetic anhydride with adipic acid in the presence of a small amount of trifluoroacetic acid. Colorless needles of pure mixed anhydride were mixed with phthalimido primaquine in chloroform in the presence of triethylamine. No reaction between the two starting materials was observed after heating at reflux for 5 days.

These experiments all seemed to indicate that some

reaction of phthalimido primaquine with acid chlorides, isocyanates, sulfonyl chlorides, or active ester did occur, however, no major reaction products could be isolated. Side reactions involving sites other than the primary and secondary amines of primaquine were considered as possibly having interfered to some degree with the preparation of the desired products.

3. Reaction of quinoline with difunctional intermediates. In order to investigate the possibility that the quinoline moiety of primaquine interfered with substitution at the secondary amine position, a number of reactions using pure quinoline were carried out. The first series of reactions were carried out at room temperature in chloroform using two to one mole ratios of quinoline to oxalyl chloride, succinyl chloride, and sebacyl chloride. The second series of reactions were carried out in acetonitrile. The results of these reactions are summarized in Table 9. As can be seen, all of the mixtures rapidly underwent reactions as indicated by the observed color changes. The reactions did not appear to be solvent specific, as the color changes were essentially the same in both solvents, however, the reactions did proceed considerably faster in the more polar acetonitrile.

TABLE 9

APPEARANCE OF REACTION MIXTURES CONTAINING QUINOLINE AND ACID CHLORIDES

Solvent	Acid Chloride		
	Oxalyl	Succinyl	Sebacyl
Chloroform	yellow	green	yellow
Acetonitrile	dark yellow	dark green	yellow

The effect of quinoline on 2,4-toluenediisocyanate (TDI) was also examined. A two to one mole ratio of quinoline and TDI were mixed in acetonitrile. Within a few minutes the initially clear solution became cloudy. A white crystalline precipitate could be observed within 20 min which rapidly increased in quantity with time. The infrared spectrum of the crystalline solid showed a strong absorbtion corresponding to N=C=O stretching at 2270 cm^{-1}, as well as one indicative of symmetric N=C=O bending at 1385 cm^{-1}. The presence of strong absorbtions at 1645, 1590, and 1550 cm^{-1} indicated the presence of variously substituted C=O groups. These absorbtions, coupled with the fact that isocyanates are known to form stable trimers, especially in the presence of tertiary amines such as pyridine and quinoline, were considered to be strong evidence of the presence of trimerized isocyanate structures. A moderate absorbtion at 810 cm^{-1} also tended to support

this identification.

The similarities observed between the reactions of acid chlorides and isocyanates with both phthalimido primaquine and quinoline indicated that the same, or chemically similar, reactions occurred. In addition, the products isolated from the reaction mixtures, particularly those from the isocyanate mixtures, seemed to be at least qualitatively the same as evidenced by their characteristic infrared absorbtions. These observations strongly supported the speculation that the difficulties encountered when trying to couple phthalimido primaquine with difunctional intermediates were due, at least in part, to interference by the quinoline group present in the primaquine derivative.

D. Preparation of primaquine biuret polymers. The difference in reactivity between the two amino groups involved prevented the use of primaquine as a diamine for the formation of high molecular weight polyamides or polyureas by one-step polycondensation techniques. In addition, reactions associated with the quinoline moiety of primaquine effectively interfered with the use of this compound in a multi-step polymerization scheme also involving both the primary and secondary amines. The use of both of the active sites available on the primary amine of primaquine to incorporate the drug into the backbone of a polymer chain

was considered as one means of circumventing these problems. This was carried out by preparing a polymer containing biuret linkages formed from equimolar ratios of diisocyanate and primaquine. This concept is illustrated in Figure 9. The polymerization, although carried out as one step, was actually a two stage reaction. The first stage involved the reaction of primaquine with diisocyanate to form the disubstituted urea as shown below:

$$2\ \text{Primaquine} - NH_2 + OCH\text{-}R\text{-}NCO \longrightarrow$$

$$\text{Primaquine-NHCONH-R-NHCONH-Primaquine}$$

The reaction of the remaining isocyanate with the active amide hydrogens in the urea formed in the first stage constituted the second stage of the reaction as shown below:

$$\text{Primaquine-NHCONH-R-NHCONH-Primaquine} + OCN\text{-}R\text{-}NCO \longrightarrow$$

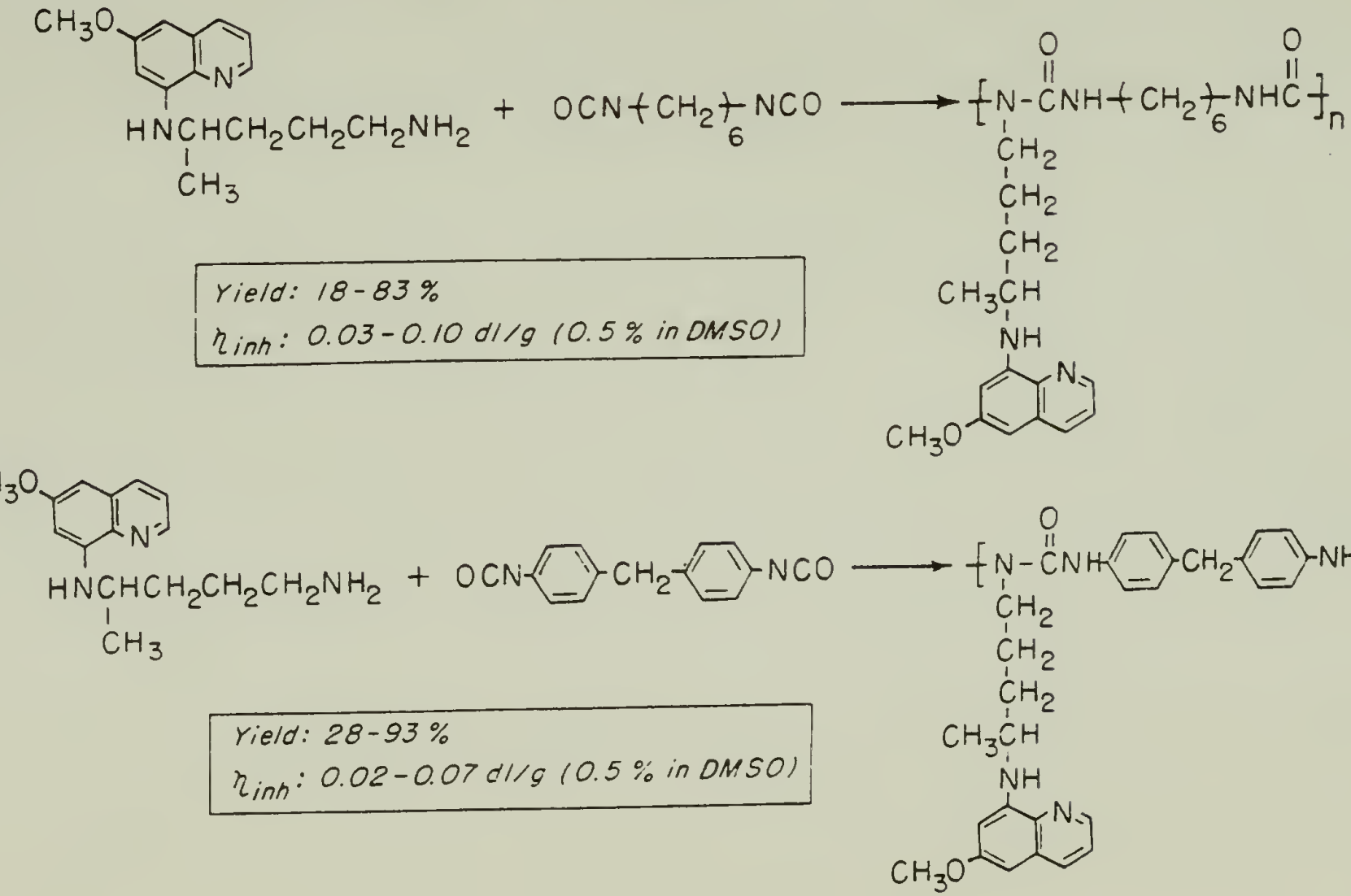
$$-\left(-\underset{\text{Primaquine}}{\underset{|}{N}}CONH\text{-}R\text{-}NHCO-\right)_n-$$

This resulted in the formation of biuret linkages along the polymer backbone.

Several polybiurets involving primaquine were prepared from HMDI in solvents such as DMSO, DMF, DMAc, and sulfolane. The polymers were isolated as beige powders in yields ranging from 20 to 80%. The molecular weights were quite low, as indicated by their inherent viscosities,

Figure 9. Synthesis of primaquine biuret polymers (one-step polymerization scheme).

One-Step Polymerization Scheme



Yield: 18-83 %
η_{inh}: 0.03-0.10 dl/g (0.5 % in DMSO)

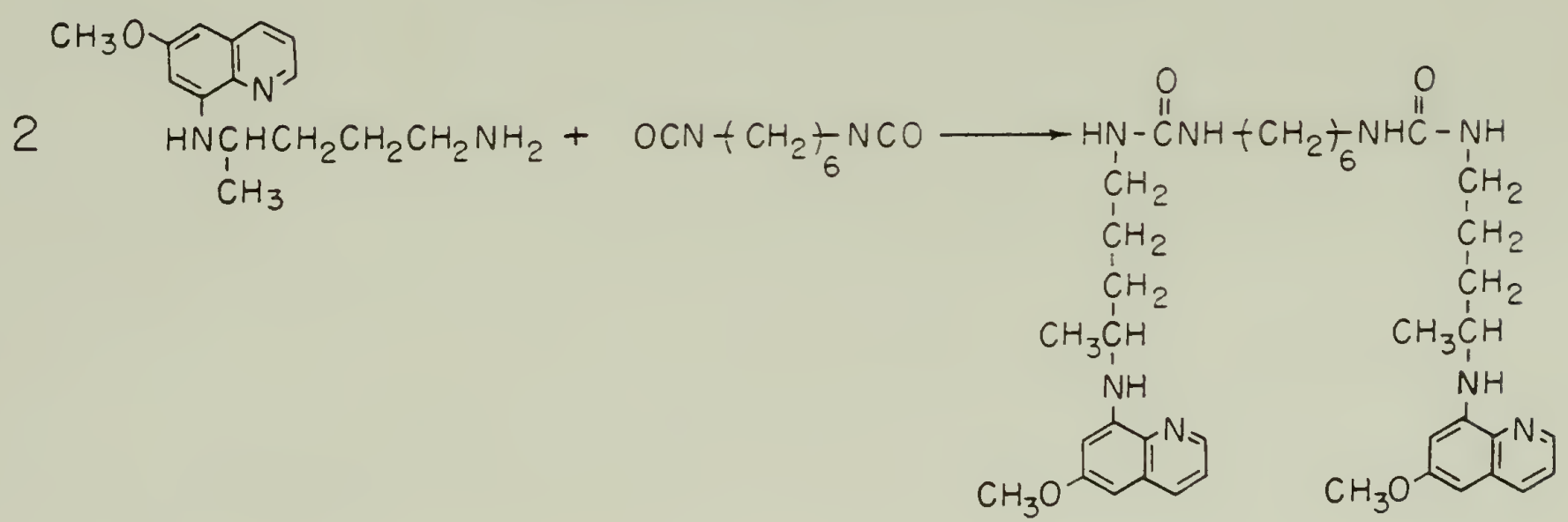
Yield: 28-93 %
η_{inh}: 0.02-0.07 dl/g (0.5 % in DMSO)

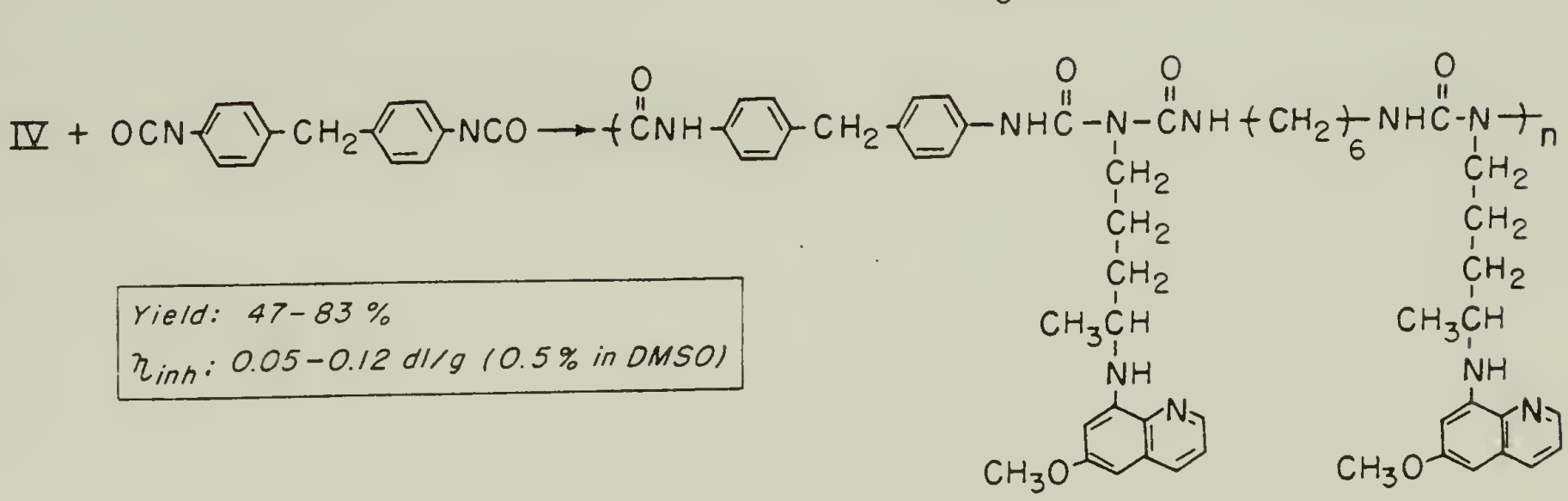
which ranged from 0.03 to 0.10 dl/g. Because aliphatic isocyanates are less reactive than aromatic isocyanates it was thought that higher molecular weights could be achieved using the aromatic MDI in place of HMDI. The results from experiments using MDI were summarized in Table 5 (p. 63), as were the results from the experiments involving HMDI.

As can be seen, low molecular weight materials were again obtained. Polybiurets obtained from MDI would tend to have very stiff backbone chains in comparison with those obtained from HMDI. This was thought to cause premature precipitation to occur in some cases before high molecular weight products could be formed, as precipitation was observed during some of the reactions. A two step polymerization involving both the flexible HMDI and the stiff, but more reactive MDI was considered as a possible means of increasing the molecular weight of the polymers. This concept is illustrated in Figure 10. It was found that the first step of the reaction, involving the addition of two moles of primaquine to one mole of HMDI, proceeded to completion almost immediately, as no residual isocyanate groups could be detected in the infrared spectrum of the reaction solution after 5 min. The second step involved the addition of another mole of MDI to the reaction mixture to form the polybiuret. The reaction was driven as far as possible to completion by heating to 90°C for 6 hr. The

Figure 10. Synthesis of primaquine biuret polymers (two-step polymerization scheme).

Two-Step Polymerization Scheme





Yield: 47–83 %

η_{inh}: 0.05–0.12 dl/g (0.5 % in DMSO)

polymers isolated using this procedure with DMF and DMSO as solvents were found to have inherent viscosities of 0.05 and 0.12 dl/g respectively (Table 5).

The infrared spectra of all of the polybiurets produced were similar, with absorbtions at 3350 cm^{-1} (N-H stretching), 2930 and 2850 cm^{-1} (C-H stretching), and 1760 cm^{-1} (C=O stretching).

It should be added that although the molecular weights of these polymers were low, this was not necessarily undesirable. Very high molecular weights are not always necessary, or even desirable, in many systems. Also, despite the fact that most pharmaceutical agents lose their activity upon multiple substitution, there is a distinct possibility that the polybiurets produced during the course of this study may be biologically active in their high molecular weight form. This is due to the fact that the primaquine incorporated into the polymer chains was done so exclusively through the primary amine. As pointed out in the introduction, 8-aminoquinoline derivatives in general, and primaquine in particular, need not remain unsubstituted on this nitrogen atom in order to retain their activity.

E. Preparation of primaquine-substituted polyepichlorohydrin. For comparative purposes primaquine was also incorporated into a polymer as a side chain. This involved the reaction

and transformation of functional groups on preformed polymers as illustrated earlier in Figure 6. In this case, the active agent, primaquine, was allowed to react with pendant alkyl chloride groups present on the backbone of the base polymer, polyepichlorohydrin. The reactions were performed at room temperature in DMF. It was found that an essentially constant content of chlorine groups remained in the polymers after the reactions independent of the amount of primaquine present in the initial mixtures. This was attributed to the formation of amine hydrochloride salts resulting from the reaction of amino groups present in the primaquine molecule with HCl released from the substitution reactions. The degree of substitution could be estimated, however, from the ratios of the integrated signal intensities of the aromatic protons to those of the ethoxy protons. It was found that up to 95% of the sites available for reaction underwent substitution (Table 6).

III. Preparation of Bithionol and Bithionol Polymers

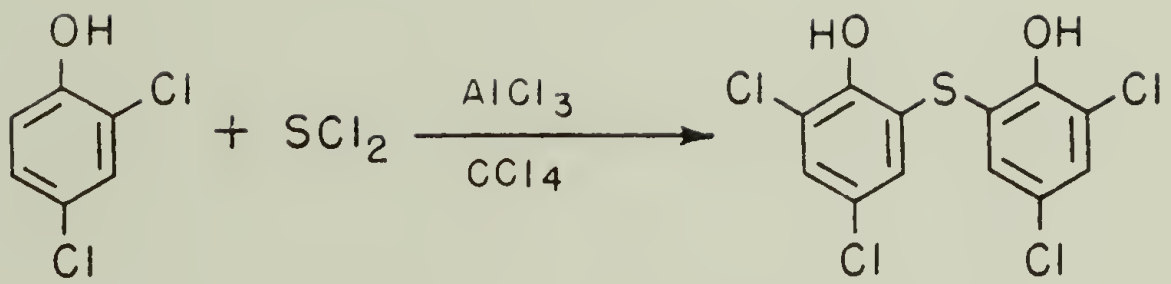
A. Introduction. Bithionol was synthesized in 43% yield from 2,4-dichlorophenol and sulfur dichloride. The bischloroformate was synthesized in 40% yield from bithionol and phosgene. A variety of polyesters, polycarbonates, polyurethanes, and three phosphorous containing polymers, each incorporating bithionol into the polymer backbone,

were prepared. Representative polymers from each of these groups were investigated with respect to their hydrolytic stability.

B. Preparation of bithionol. Bithionol was prepared according to the procedure of Cooper and Godfrey[141] (Figure 11). 2,4-Dichlorophenol and sulfur dichloride were condensed in carbon tetrachloride using an aluminum chloride catalyst to give 43% of colorless needles after recrystallization (mp 187-8°C). The infrared and ^{1}H NMR spectra were identical to those presented in the literature.[146,147] The ultraviolet spectrum was recorded in an aqueous buffer at pH 10.0. Absorbtion maxima were observed at 318 and 226 nm with molar extinction coefficients of 1.58×10^{4} and 6.75×10^{4} liter·mole^{-1}·cm^{-1}, respectively. In methanol solution bithionol has been shown[148] to have absorbtion maxima at 307 and 208.5 nm. The bathochromic shift of absorbtion maxima in dilute base can be attributed to the additional pair of nonbonding electrons in the phenolate anion that are available for interaction with the π-electron system of the ring.

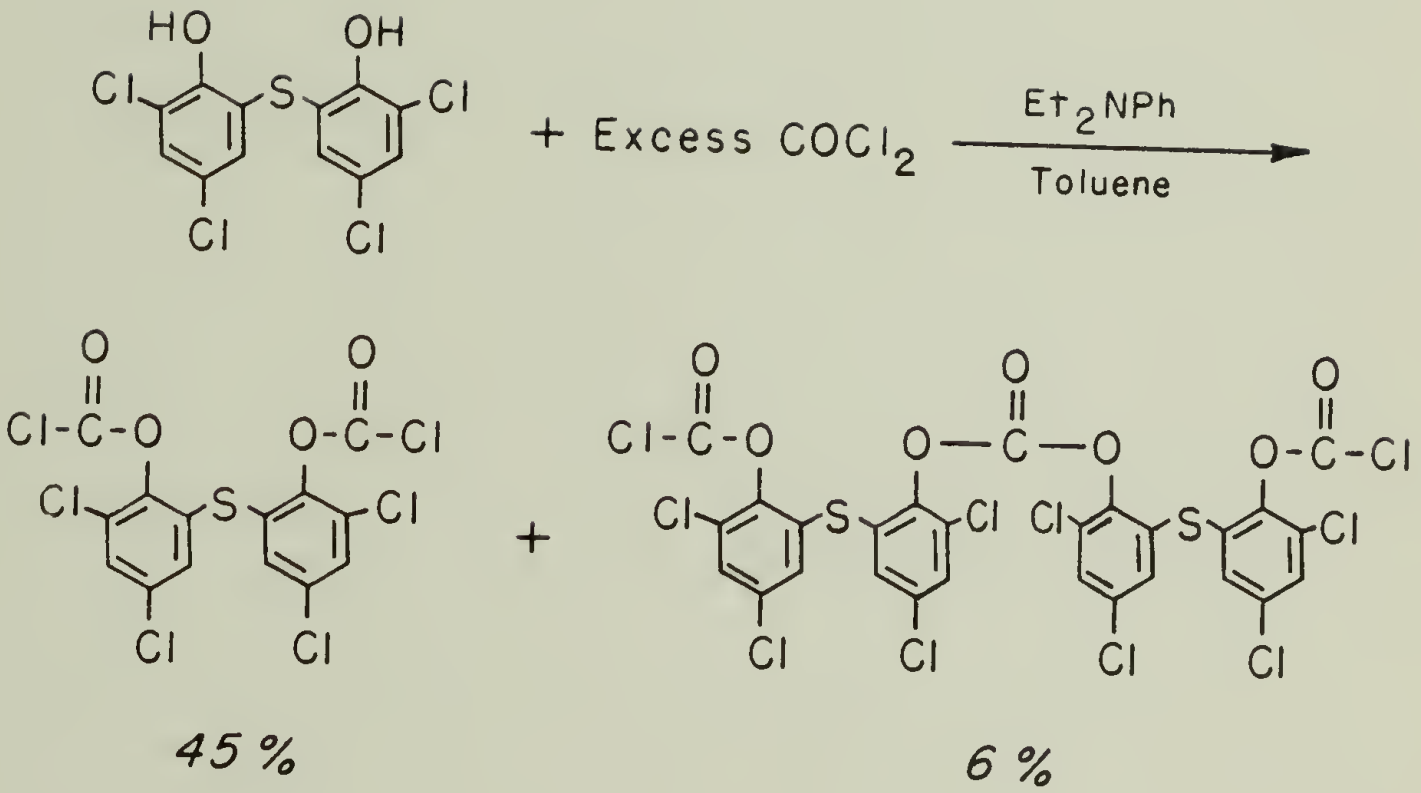
C. Preparation of bithionol bischloroformate and bithionol carbonate bischloroformate. The method of Oesper, Broker, and Cook[142] was modified for the preparation of bithionol bischloroformate (Figure 12). An N-N-diethylaniline catalyst was added to a mixture of phosgene and bithionol in

Figure 11. Synthesis of bithionol.



50 %

Figure 12. Synthesis of bithionol bischloroformate.


HO
OH
Cl
S
Cl
Cl
Cl
+ Excess $COCl_2$
Et_2NPh
Toluene
O
Cl-C-O
O-C-Cl
Cl
S
Cl
Cl
Cl
+
O—C—O
45 %
6 %

toluene over a period of 2 hr. During the first stages of catalyst addition, the initially thick suspension became considerably clearer, presumably due to the formation of bithionol phenoxide ions, which subsequently dissolved in the solution. After several more minutes, however, a fresh white precipitate could be observed forming in the mixture. This was later found to be the water soluble diethylaniline hydrochloride. After the reaction was complete (total reaction time 3 hr), the excess phosgene was removed with the aid of an aspirator. The contents of the reaction flask were protected with a paraffin oil bubbler and a large trap between the reaction flask and the aspirator. Slight warming of the contents of the flask during the final stages of phosgene removal facilitated the elimination of the last traces of the gas. The use of a vacuum pump for this step, although applicable in some circumstances, was rejected on the grounds of laboratory safety.

The viscous oil, obtained after concentrating the reaction mixture filtrate, was found to be a mixture of bithionol bischloroformate and bithionol carbonate bischloroformate ("bithionol bischloroformate dimer"). The latter compound was selectively removed by dissolving the oil in boiling n-hexane and cooling slowly. The resultant crystals had a melting point of 174-9°C and were obtained in 6% yield. The infrared spectrum of the crystals displayed a broad carbonyl absorbtion centered around 1805 cm^{-1}

with shoulders at 1815 and 1790 cm^{-1}, a pattern indicative of a compound containing both carbonate and chloroformate groups. A slight absorbtion corresponding to aromatic C-H stretching was observed at 3060 cm^{-1} Aromatic C-C stretching produced an absorbtion at 1420 cm^{-1} and C-O stretching resulted in absorbtions at 1155 and 1110 cm^{-1}. The ^{1}H NMR spectrum showed the expected nonsymmetrical aromatic absorbtions at δ 6.9 and 7.3.

After the removal of the bithionol carbonate bis-chloroformate, the remaining material was found to be difficult to recrystallize. When left in a sealed flask, however, the oil gradually became more viscous and crystals were observed growing spontaneously after 8 days. After a total of 13 days the entire contents of the flask became a solid mass of crystals. These crystals were purified by dissolving in boiling n-pentane and cooling slowly. A few seed crystals added to the cooled solution facilitated crystallization. The resulting purified product was obtained in 40% yield and was shown to be bithionol bis-chloroformate with a carbonyl absorbtion in the infrared at 1780 cm^{-1}, indicative of a chloroformate. The absorbtion due to C-O stretching appeared as a strong broad peak centered at 1090 cm^{-1}. The ^{1}H NMR spectrum showed symmetrical absorbtions at δ 7.1 and 7.3 as expected.

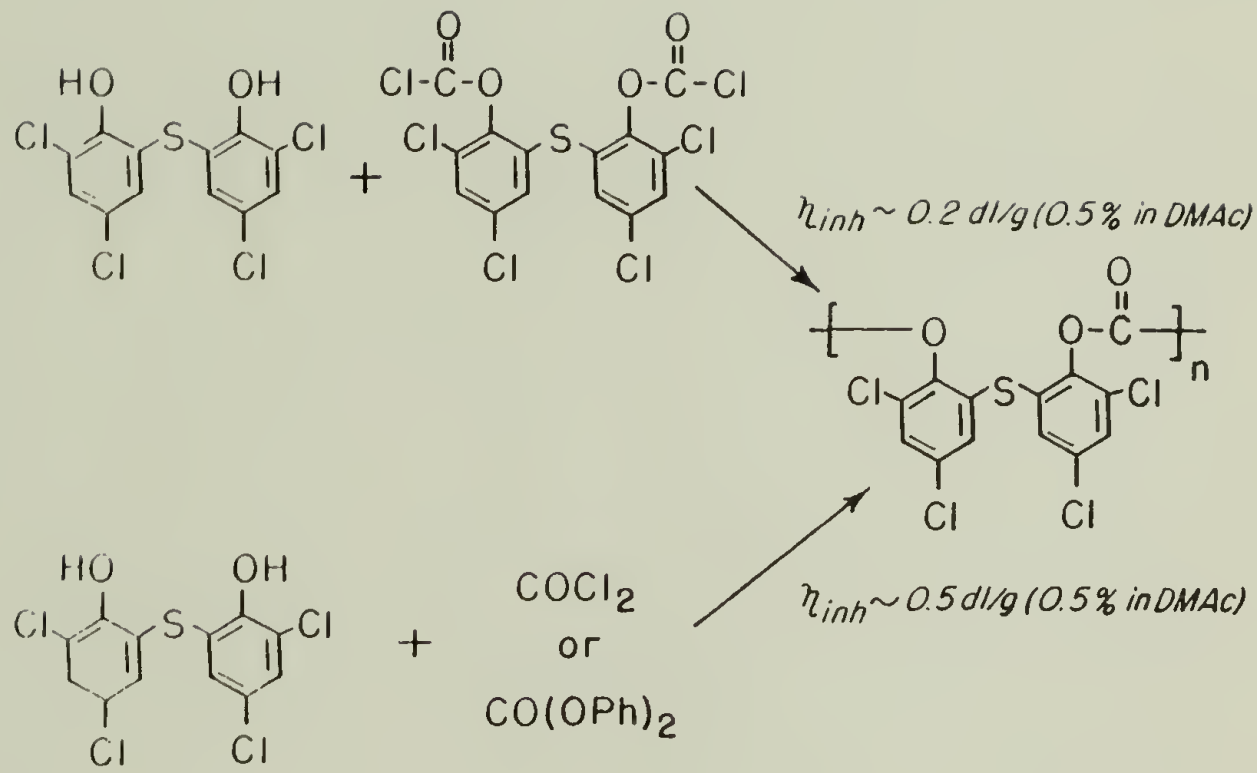
The identity of the two products isolated from the reaction mixture was confirmed by microanalysis as well as

by characterizing the dimethyl esters of each. Each compound was reacted with an excess of methanol for 24 hr, then concentrated to a solid under reduced pressure. The ^{1}H NMR spectrum of one ester showed a 1.0 to 1.5 ratio of aromatic to aliphatic protons, equivalent to the theoretical for bithionol bis(methyl carbonate). The second ester showed a respective 1.3 to 1.0 ratio, equivalent to the theoretical for bithionol carbonate bis(methyl carbonate).

D. Preparation of bithionol polycarbonate. Bithionol polycarbonate was prepared using several different polymerization reactions and techniques as illustrated in Figure 13. The stirred interfacial polymerization of bithionol and bithionol bischloroformate in a water/methylene chloride system gave polycarbonate with an inherent viscosity of 0.16 dl/g in 44% yield. The low yield was attributed to partial hydrolysis of the monomer.

Polymerization in solution was also utilized for the preparation of bithionol polycarbonate. Polymerization in methylene chloride with pyridine as an acid acceptor gave a 90% yield of polymer with an inherent viscosity of 0.17 dl/g. The polymer precipitated from solution, however, and was later found to be insoluble in most common organic solvents. It was soluble in DMF, DMAc, and phenol/1,2-dichloroethane (60/40 by wt). The relatively low molecular weight of the material was considered to be

Figure 13. Synthesis of bithionol polycarbonate.


HO
OH
Cl
S
Cl
Cl
Cl
Cl-C-O
O-C-Cl
Cl
S
Cl
Cl
Cl
η_{inh} ~ 0.2 dl/g (0.5% in DMAc)
O
O-C
n
Cl
S
Cl
Cl
Cl
HO
OH
Cl
S
Cl
Cl
Cl
$COCl_2$
or
$CO(OPh)_2$
η_{inh} ~ 0.5 dl/g (0.5% in DMAc)

a result of two factors. On the one hand, the bischloroformate was thought to have reacted to some degree with pyridine, a tertiary amine. This reaction has been well documented.[149-152] The precipitation of polymer prior to achievement of high molecular weight was also thought to contribute to the low molecular weight obtained. The formation of bithionol phenoxide ion upon addition of pyridine was indicated by the dissolving of the insoluble bithionol crystals and the appearance of a pale pink color in the solution. The color disappeared, however, as a precipitate formed, indicating that reaction was indeed occurring between the bithionol phenoxide and the bischloroformate present. In order to minimize reaction between the bischloroformate and the tertiary amine present, collidine, a sterically hindered derivative of pyridine, was tried as the acid acceptor in place of pyridine in the solution polymerization. The use of this amine gave polycarbonate with an inherent viscosity of 0.20 dl/g in a 96% yield. Although both the viscosity and yield were slightly higher than that obtained with the use of pyridine, the increase was not thought to be significant. At this point, the major difficulty in the polymerization seemed to be the insolubility of the polymer product and its premature precipitation. Consequently, DMAc was used as a medium for the polymerization, however, no appreciable difference in the molecular weight of the polycarbonate was noted, al-

though there was a significant decrease in yield. Reaction of chloroformate groups with the amide solvent was believed to be responsible for the decrease in yield.

The use of melt polymerization techniques gave polycarbonate of consistently higher molecular weight than either interfacial or solution techniques. When bithionol and a 2% excess of bithionol bischloroformate were heated together under vacuum for a total of 7 hours at temperatures up to 228°C, slightly colored polymer with an inherent viscosity of 0.35 dl/g was produced in 84% yield. Using the more conventional intermediate for the production of polycarbonate, diphenyl carbonate, with bithionol and a zinc oxide catalyst, polymer with an inherent viscosity of 0.46 dl/g was produced in 88% yield. Temperatures of 210-235°C and pressures down to 3 mm were used to remove the byproduct phenol from the reaction mixture. The polycarbonate, although much higher in molecular weight than those produced by other techniques, had poor mechanical properties. It was brittle and crumbled easily, despite the fact that it could be drawn into thin fibers directly from the melt. A glass transition temperature was detected by differential scanning calorimetry at 105°C. The infrared spectrum of the polycarbonate showed residual phenolic O-H stretching around 3430 cm^{-1}, indicating the presence of bithionol end groups. A slight absorbtion at 3075 cm^{-1} due to aromatic C-H stretching was noted, and a carbonyl

absorbtion at 1810 cm^{-1} was also observed. Aromatic C-C stretching and C-O stretching produced absorbtions at 1420 and 1115 cm^{-1}, respectively. The ^1H NMR spectrum showed the expected peaks due to the aromatic protons at δ 7.0 and 7.3. A small doublet centered around δ 2.8 could be assigned to residual protons present in the d_7-DMF solvent. It should be noted that the polycarbonate produced using the different techniques described above gave essentially identical infrared and ^1H NMR spectra. The results from the different synthetic procedures used are summarized in Table 10.

TABLE 10

PREPARATION OF BITHIONOL POLYCARBONATE

Polymerization Technique[a]	Yield in %	η_{inh}[b] in dl/g
CH_2Cl_2/H_2O interfacial	44	0.16
CH_2Cl_2/pyridine solution	90	0.17
CH_2Cl_2/collidine solution	96	0.20
DMAc/pyridine solution	18	0.17
Melt	84	0.35
Melt[c]	88	0.46

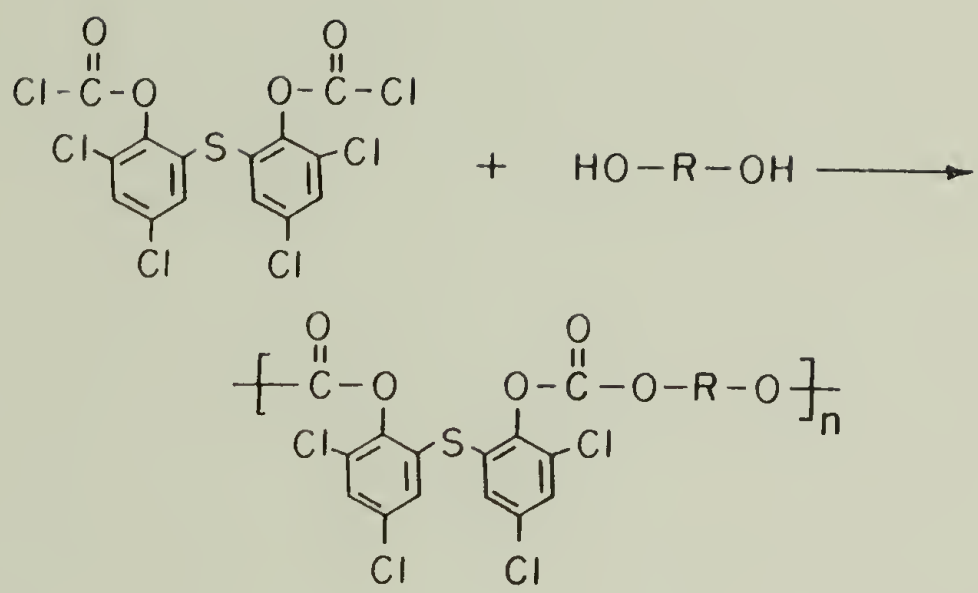
(a) bithionol + bithionol bischloroformate

(b) 0.5% in DMAc

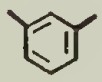
(c) bithionol + diphenyl carbonate

E. Preparation of bithionol alternating copolycarbonates. Bithionol alternating copolycarbonates were prepared from bithionol bischloroformate and several diols in a methylene chloride solution with pyridine present as an acid acceptor. The reaction scheme is illustrated in Figure 14. The yields and inherent viscosities of the alternating polycarbonates obtained were similar in all cases, ranging from 70 to 90% and from 0.16 to 0.22 dl/g respectively (Table 11). Identical procedures were used for the preparation of each of the alternating copolycarbonates which utilized ethylene glycol, 1,10-decanediol, resorcinol, isopropylidenediphenol, and 4,4'-thiobis(6-tert-butyl-o-cresol) as the diol components. The pyridine solution that was added to each reaction mixture was from a premixed stock solution consisting of 19.4 ml (19.37g, 0.25 mmole) pyridine diluted to volume with methylene chloride in a 100 ml volumetric flask.

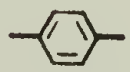
Figure 14. Synthesis of bithionol alternating copolycarbonates.



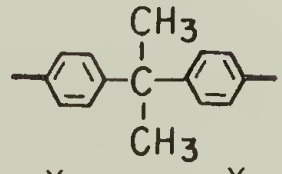
R = $-(CH_2)_2-$



$-(CH_2)_3-$



$-(CH_2)_4-$



$-(CH_2)_6-$

$-(CH_2)_{10}-$

$-O-(CH_2CH_2-O)_m-$

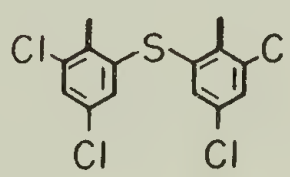


TABLE 11

PREPARATION OF BITHIONOL ALTERNATING COPOLYCARBONATES FROM BITHIONOL BISCHLOROFORMATE AND DIOL

Diol	Yield in %	η_{inh}(a) in dl/g
Ethylene glycol	70	0.16
1,10-Decanediol	79	0.22
Resorcinol	71	0.17
Isopropylidenediphenol	90	0.21
4,4'-Thiobis(6-tert-butyl-o-cresol)	72	0.19
Bithionol	90	0.17

(a) 0.5% in DMAc

Although each reaction was run simultaneously and under identical conditions, some variations were observed during the course of the procedure. The mixture with ethylene glycol, for instance, remained clear and colorless throughout the reaction with no precipitate formation. The 1,10-decanediol, on the other hand, was only partially soluble in methylene chloride, which resulted in an initial suspension of diol crystals in the reaction solution. With the addition of pyridine, however, these crystals dissolved slowly and a pale pink color formed. Both the color and the solubilization of the diol was attributed to the presence of the pyridine base. As the reaction proceeded, however, the pink color vanished. This observation was

consistent with the formation of polymer from an alkoxide and a bischloroformate. The mixture containing resorcinol was similar in appearance to the one containing 1,10-decanediol. The color observed during the initial stages of the reaction, however, was a pale yellow. As before, the color disappeared as the reaction progressed and no precipitate was formed. The use of isopropylidenediphenol, on the other hand, gave a clear, colorless, reaction mixture throughout. 4,4'Thiobis(6-tert-butyl-o-cresol), however, gave a brown color upon addition of pyridine. This color eventually turned to a red, but did not completely disappear. Bisphenols of this type, common as antioxidants, are known to produce phenoxide ions of intense color, particularly when electron donating groups, such as alkyl groups, are ortho and/or para to the phenoxide chromophore.

The infrared spectra of each of the alternating copolycarbonates produced were very similar. The polymers derived from alkyl diols (ethylene glycol and 1,10-decanediol) both showed absorbtions attributed to C-H stretching at 2930 and 2850 cm^{-1}. The carbonyl absorbtion was observed at 1770 cm^{-1}. The polymers derived from bisphenols (resorcinol, isopropylidene diphenol, and 4,4'-thiobis(6-tert-butyl-o-cresol)), on the other hand, displayed an aromatic C-H stretching absorbtion at 3075 cm^{-1} along with a carbonyl absorbtion at 1785 cm^{-1}. These positions are typical for aromatic/aromatic polycarbonates. Additional

absorbtions at 2930 and 2860 cm^{-1} due to the aliphatic C-H stretching of the methyl and tert-butyl groups were also shown by the bithionol/4,4'-thiobis(6-tert-butyl-o-cresol) alternating copolycarbonate.

F. Preparation of bithionol/polyethylene glycol alternating copolycarbonates. Six bithionol alternating copolycarbonates were synthesized from bithionol bischloroformate using hydrophilic polyethylene glycols as alternating comonomers. The polyethylene glycols (PEG's) used were: ethylene glycol, tetraethylene glycol, Carbowax PEG 400, Carbowax PEG 600, Carbowax PEG 1000, and Carbowax PEG 4000. The polymers were all synthesized under the same conditions using a melt polycondensation technique.

All of the mixtures had similar appearances throughout the period of reaction. The temperature and pressure were varied from 98 to 180°C and from atmospheric to 3 mm over a total of 18 hr. Bubbles of byproduct HCl could be seen escaping from the viscous reaction mixtures as the reactions proceeded. All of the resultant polymers were light brown in color. The copolycarbonates prepared from ethylene glycol and tetraethylene glycol were both hard glasses while that produced from PEG 400 was a tough leathery polymer. Tacky polymers were produced from PEG's 600 and 1000, and a waxy solid was obtained from PEG 4000. Table 12 shows the yields and inherent viscosities obtained

from each of the reactions. All of the reactions gave products in essentially quantitative conversion (yields: 86-99%). The inherent viscosities varied from 0.43 dl/g for the ethylene glycol copolycarbonate to 1.22 dl/g for the PEG 4000 copolycarbonate.

TABLE 12

PREPARATION OF BITHIONOL/POLYETHYLENE GLYCOL ALTERNATING COPOLYCARBONATES

Polyethylene Glycol	Yield in %	η_{inh} (a) in dl/g
Ethylene glycol	96	0.43
Tetraethylene glycol (PEG 200)	99	0.79
PEG 400	93	0.64
PEG 600	97	0.81
PEG 1000	93	0.85
PEG 4000	86	1.22

(a) 0.5% in DMAc

Despite the wide range of lengths of polyethylene glycol segments incorporated into the polymers, only the copolycarbonate prepared from PEG 4000 was completely water soluble. The polymer obtained from PEG 1000 seemed to swell in water to some degree, however, it remained insoluble. All the others were found to be completely water insoluble.

The infrared spectra of all of the alternating

copolycarbonates were similar with absorbtions attributed to aliphatic C-H stretching around 2890 cm^{-1}, C=O stretching at 1770 cm^{-1} and C-O stretching around 1110 cm^{-1}. The copolycarbonates from ethylene glycol and tetraethylene glycol also showed aliphatic C-H stretching absorbtions at 2930 and 2840 cm^{-1} respectively, as well as small aromatic C-H stretching absorbtions at 3060 cm^{-1}. The ^{1}H NMR spectra of the ethylene glycol copolymer showed a multiple centered at δ 4.2 due to the $\underline{CH}_2$-O-$\overset{O}{\overset{\|}{C}}$ protons and a multiplet due to the aromatic protons centered at δ 7.4 The copolymer prepared from tetraethylene glycol gave peaks in essentially the same positions, however a large multiplet attributed to absorbtion by ethoxy methylene protons was also observed at δ 3.4-3.8. This was also true of the PEG 400 and 600 copolycarbonates. Although aromatic protons were present in all the polymers, peaks associated with these protons could not be observed in the polymers containing PEG 1000 or PEG 4000 units. This was not surprising, as ratios of aromatic to aliphatic protons of 1 to 20 and 1 to 80, respectively, were expected on the basis of their proposed structures.

G. Preparation of bithionol terpolycarbonates containing PEG 4000. Ten terpolycarbonates were prepared, each polycarbonate containing bithionol, PEG 4000, and an additional diol segment. The inclusion of the hydrophilic PEG 4000

segment was intended to render the polymers water soluble. The polymers were prepared from bithionol bischloroformate and an equimolar ratio of Carbowax PEG 4000 and a diol using a melt polycondensation procedure. The diols used were ethylene glycol, 1,3-propanediol, 1,4-butanediol, 1,6-hexanediol, 1,10-decanediol, resorcinol, hydroquinone, isopropylidenediphenol, 4,4'-thiobis(6-tert-butyl-o-cresol), and bithionol. The reaction mixtures containing the aliphatic diols were kept at 105°C for 6.5 hr then at 194°C for 2.5 hr. The initial atmospheric pressure was then reduced to 20 mm where it was kept for an additional 12 hr, after which it was lowered again to 3 mm and kept for 3 hr, still at 194°C. In contrast, the reaction mixtures containing the bisphenols were kept at 205°C for a total of 24 hr during which time the pressure was reduced from atmospheric to 3 mm as described in the Experimental Section. The lower temperatures and pressures used for the mixtures containing the aliphatic diols were intended to minimize vaporization of the more volatile components. Despite the use of nitrogen in the reaction, some degradation of the polymer occurred during the procedure as evidenced by the light brown color of the products. High molecular weight polymers were nevertheless produced as shown in Table 13. The reaction mixtures containing aliphatic diols produced polymers in consistently higher yields and of higher viscosities than those containing

TABLE 13

PREPARATION OF BITHIONOL TERPOLYCARBONATES CONTAINING PEG 4000

Diol Comonomer	Yield in %	η_{inh} (a) in dl/g
Ethylene glycol	51	0.44
1,3-Propanediol	56	0.53
1,4-Butanediol	85	0.76
1,6-Hexanediol	92	0.78
1,10-Decanediol	95	0.96
Resorcinol	18	0.48
Hydroquinone	15	0.41
Isopropylidinediphenol	22	0.51
4,4'-Thiobis(6-tert-butyl-o-cresol)	22	0.55
Bithionol	20	0.49

(a) 0.5% in DMAc

aromatic bisphenols. This was not surprising considering the greater reactivity of aliphatic alcohols as compared to phenols.

Elemental analysis of two of the polymers indicated that PEG 4000 was incorporated into the polymers to different degrees. The bithionol/1,10-decanediol/PEG 4000 terpolycarbonate was found to contain 8.10% Cl, indicating that 1,10-decanediol and PEG 4000 were incorporated into the polymer in a 7 to 93 mole ratio, each unit connected with bithionol biscarbonate linkages. This was in contrast to the bithionol/resorcinol/PEG 4000 terpolycarbonate which was found to have a Cl content of 19.43%. Less PEG 4000 was incorporated into this polymer, as the ratio of resorcinol to PEG 4000 in the polymer was calculated to be 70 to 30.

Both the infrared and ^{1}H NMR spectra of the terpolycarbonates were dominated by the presence of the large amounts of polyoxyethylene segments present. The infrared spectra of the polymers displayed absorbtions originating from aliphatic C-H stretching at 2870 or 2875 cm^{-1}, C=O stretching at 1775 or 1770 cm^{-1}, and C-O stretching at 1120 or 1115 cm^{-1}. The ^{1}H NMR spectra showed the expected single absorbtion at δ 3.4 which was attributed to ethoxy methylene protons.

H. Preparation of bithionol alternating copolyurethanes.

The reaction between a bischloroformate and a diamine can

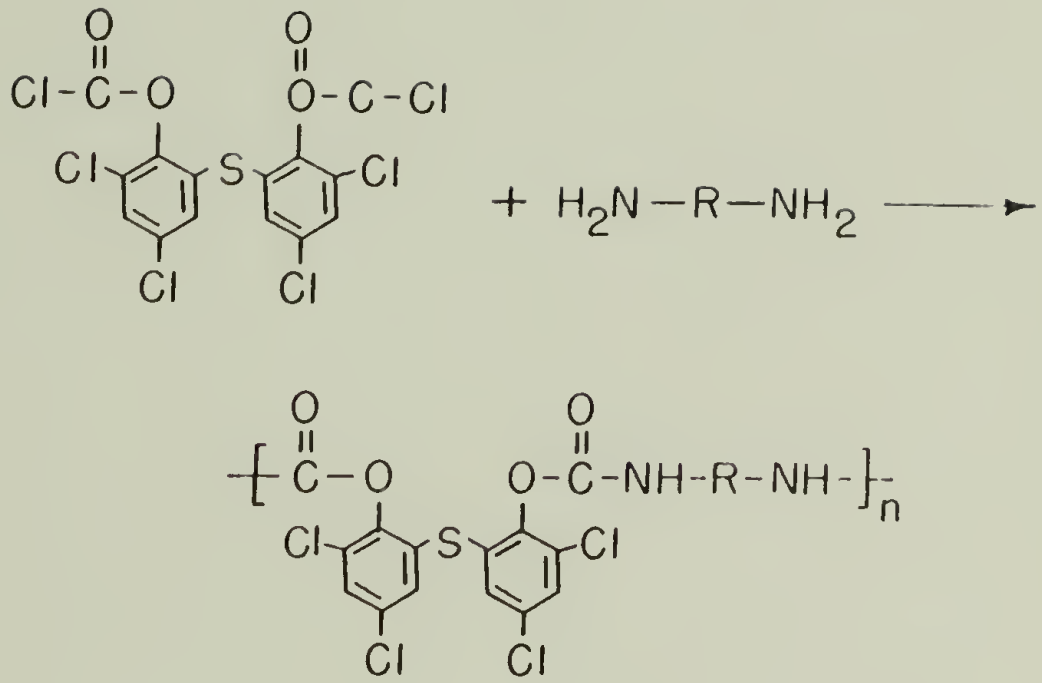
be utilized to produce polyurethanes in high molecular weight. Bithionol bischloroformate was therefore used to prepare alternating copolyurethanes from four different diamines. The diamines used were ethylenediamine, 1,10-decanediamine, m-phenylenediamine, and methylenedianiline. The reaction is illustrated in Figure 15. The polymers were synthesized using a solution polymerization technique with methylene chloride as the solvent and an excess of diamine as the acid acceptor. As shown in Table 14, the polyurethanes prepared from the more flexible diamines, 1,10-decanediamine and methylenedianiline, were both produced in quantitative yield and were much more soluble in organic solvents such as chloroform and DMAc. The more rigid polyurethanes made from ethylenediamine and m-phenylenediamine were only produced in 51% and 31% yields respectively. This was attributed to the decreased solubility of these polymers in the methylene chloride solvent.

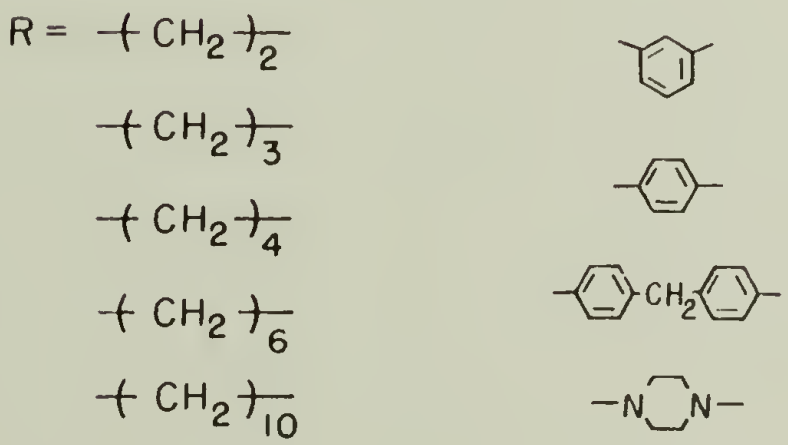
TABLE 14

PREPARATION OF BITHIONOL ALTERNATING COPOLYURETHANES FROM BITHIONOL BISCHLOROFORMATE AND DIAMINE

Diamine	Yield in %	η_{inh} [a] in dl/g
Ethylenediamine	51	0.17
1,10-Decanediamine	100	0.21
m-Phenylenediamine	31	0.27
Methylenedianiline	100	0.24

Figure 15. Synthesis of bithionol alternating copolyurethanes.





The aliphatic/aromatic alternating copolyurethanes, that is, those containing the ethylenediamine and 1,10-decanediamine segments, displayed absorbances in the infrared around 3380 cm^{-1} and at 2920 and 2850 cm^{-1} corresponding to N-H and C-H stretching respectively. A carbonyl absorbtion at 1735 cm^{-1} and an absorbtion at 1215 cm^{-1} attributed to C-O stretching was also observed. The ^{1}H NMR spectra of these polymers were also similar, consisting of a multiplet centered at δ 7.6 due to aromatic protons and broad signals centered at δ 1.2 and 3.1 attributed to internal methylene protons and protons adjacent to the urethane group, respectively. The infrared spectra of the aromatic/aromatic copolyurethanes, on the other hand, showed absorbtions corresponding to N-H stretching at 3420 and 3300 cm^{-1}, aromatic C-H stretching at 3075 cm^{-1}, C=O stretching around 1760 cm^{-1}, and C-O stretching at 1200 cm^{-1}. The ^{1}H NMR spectra of these polymers showed overlapping peaks from δ 6.9 to 8.0. The alternating copolyurethane based on methylenedianiline also displayed an additional singlet attributed to the methylene protons at δ 4.1. A weak doublet centered around δ 2.75 appearing in the ^{1}H NMR spectra of both the aliphatic and the aromatic copolyurethanes was found to be due to residual proton impurities in the d_7-DMF solvent.

For comparative purposes, an alternating copolyurethane with a structure identical to that obtained from

the reaction of bithionol bischloroformate and methylenedianiline was prepared from bithionol and 4,4'-diisocyanodiphenylmethane (MDI) in DMAc solution. Although the polymer was obtained in high yield (94%), the molecular weight was extremely low as indicated by an inherent viscosity of 0.06 dl/g. This was not unexpected, however, as isocyanates generally do not form high molecular weight polymers with bisphenols. This has been attributed to the greater acidity of phenols compared to aliphatic alcohols. In the case of bithionol, the acidity is particularly great because of the electron withdrawing nature of the four chlorine substituents.

I. Preparation of bithionol copolyurethanes containing PEG 4000. In order to increase the solubility of the bithionol copolyurethanes in aqueous environments Carbowax PEG 4000 was incorporated into the polymers. This was accomplished by condensing bithionol bischloroformate with an equimolar ratio of Carbowax PEG 4000 and a diamine in solution. Calcium hydroxide was used as an acid acceptor. A variety of diamines were used, including ethylenediamine, 1,3-propanediamine, 1,4-butanediamine, 1,6-hexanediamine, 1,10-decanediamine, m- and p-phenylenediamine, methylenedianiline, and piperazine. The reactions were rapid and the resultant reaction mixtures became viscous within a few minutes. The polymer solutions were poured into

methanol containing a small amount of HCl. Although some of the polymer fractions containing large amounts of incorporated PEG 4000 segments undoubtedly failed to precipitate and remained in the methanol solution, this procedure was the only effective technique which allowed for the removal of unreacted monomers, byproducts, and other impurities. The polymer fractions that did precipitate were isolated by centrifugation. All of the resultant copolyurethanes were off-white powders that were found to be swellable, but not soluble, in water. Thin layer chromatography did not reveal any low molecular weight impurities. The assumption that polymer fractions containing large amounts of incorporated PEG 4000 segments were lost due to their solubility in the precipitating medium was substantiated by the microanalysis of two of the polymers. The material derived from 1,10-decanediamine was found to contain 22.86% Cl, which corresponded to a polymer containing 78% 1,10-decanediamine and 22% PEG 4000 as comonomer units. Each unit was connected with a linkage derived from bithionol bischloroformate. The material derived from m-phenylenediamine, on the other hand, was found to contain 21.66% Cl, which corresponded to a polymer containing 75% m-phenylenediamine and 25% PEG 4000 as comonomers. These results were consistent with the possibility of polymer fractionation during purification.

The yields and inherent viscosities of the polymers

produced in this manner are shown in Table 15. As with the copolycarbonates, the highest yields and molecular weights were achieved using long chain aliphatic comonomers.

The infrared spectra of the copolyurethanes containing aliphatic diamine segments displayed a strong absorbtion in the N-H stretching region around 3400 and 3350 cm^{-1}, as well as in the aromatic and aliphatic C-H stretching regions near 3075 cm^{-1} and 2920 and 2860 cm^{-1}, respectively. Carbonyl and C-O stretching absorbtions were also observed at 1780 and 1240 and 1215 cm^{-1} respectively. The infrared spectra of the polymers containing aromatic diamine segments were similar to those described above, however, the absorbtions in the N-H and aliphatic C-H stretching regions were weaker. The ^{1}H NMR spectra of the polymers were similar in that they were all dominated by a single peak at δ 3.4 attributed to the large number of ethoxy methylene protons present.

J. Preparation of bithionol polyesters. In order to produce a variety of bithionol polyesters, the acid chlorides of oxalic, malonic, succinic, fumaric, adipic, sebacic, isophthalic, and terephthalic acids were individually mixed with an equimolar portion of bithionol in chloroform with tributylamine present as an acid acceptor (Figure 16). All of the mixtures formed precipitates during the course of the polymerization reactions. The mixture containing

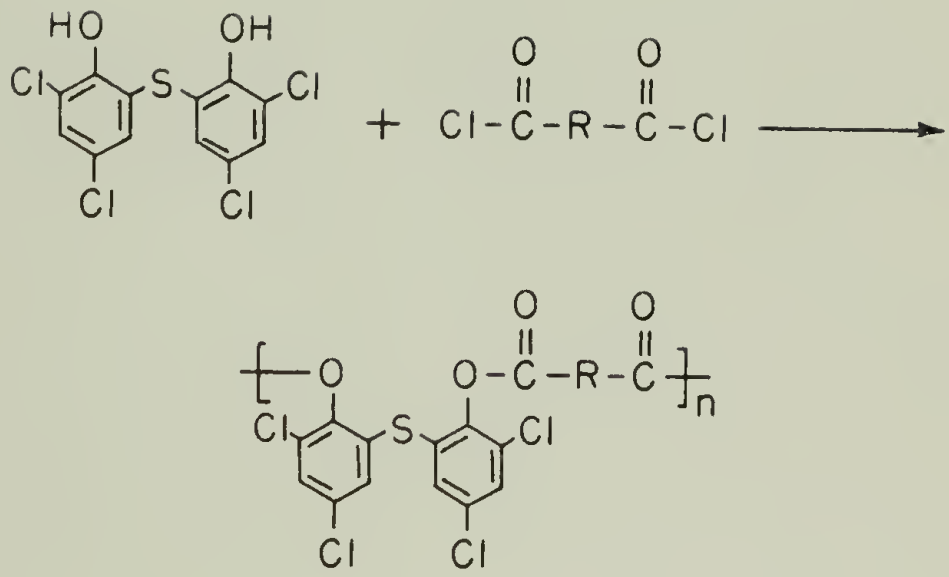
TABLE 15

PREPARATION OF BITHIONOL COPOLYURETHANES CONTAINING PEG 4000

Diamine Comonomer	Yield in %	η_{inh} (a) in dl/g
Ethylenediamine	36	0.31
1,3-Propanediamine	41	0.30
1,4-Butanediamine	56	0.39
1,6-Hexanediamine	81	0.60
1,10-Decanediamine	93	0.64
m-Phenylenediamine	48	0.57
p-Phenylenediamine	43	0.44
Methylenedianiline	60	0.61
Piperazine	42	0.40

(a) 0.5% in DMAc

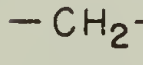
Figure 16. Synthesis of bithionol polyesters.



R = Oxalate

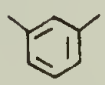
$-CH_2-$

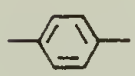
$-CH_2CH_2-$



$-(CH_2)_4-$

$-(CH_2)_8-$





oxalyl chloride formed a white precipitate within a few minutes, while the mixtures containing malonyl and succinyl chloride formed orange and dark blue-black precipitates respectively, also within a few minutes. The presence of fumaryl chloride, however, caused an immediate thickening of the reaction mixture with the formation of a dark solid mass. Rapid reactions of that type are characteristic of highly reactive aliphatic acid chlorides. The immediate formation of precipitate was an indication of the insolubility of even low molecular weight polymers. The formation of colored reaction mixtures was indicative of the presence of numerous side reactions, also characteristic of very reactive intermediates. When the more flexible and less reactive adipoyl and sebacoyl chlorides were used, however, precipitates formed much less readily, and were much more swollen in the reaction media. The precipitates from the reactions of bithionol with isophthaloyl and terephthaloyl chloride were also fairly slow in forming and were white in color. The yield and inherent viscosity of the product isolated from each of the reaction mixtures is listed in Table 16. As can be seen, extremely low molecular weight materials were obtained in all cases, with the exception of the product from the reaction of bithionol and sebacoyl chloride, which had an inherent viscosity of 0.18 dl/g. This result was consistent with the increased solubility of the reaction product and the lower reactivity of

TABLE 16

PREPARATION OF BITHIONOL POLYESTERS FROM BITHIONOL AND ACID CHLORIDE

Acid Chloride	Yield in %	η_{inh} (a) in dl/g
Oxalyl	60	0.08
Malonyl	55	0.05
Succinyl	86	0.07
Fumaryl	78	0.03
Adipoyl	52	0.08
Sebacyl	85	0.18
Isophthaloyl	97	0.02
Terephthaloyl	92	insoluble

(a) 0.5% in DMAc

the acid chloride used in the reaction.

The technique used to prepare bithionol polyesters was also found to have a great influence on both the yield and molecular weight of the polymers. As can be seen from the data in Table 17, both solution and interfacial polymerization techniques gave low molecular weight products, although the yields of polymer were nearly quantitative. It was found that higher molecular weight bithionol polyesters could be prepared by a melt polycondensation procedure, however. This technique utilized the dimethyl esters of sebacic and isophthalic acids in place of the respective acid chlorides. The melt polycondensations were performed at 205°C. After 6 hr at atmospheric pressure nearly all of the byproduct methanol had distilled from the reaction mixtures, after which the pressure was lowered to 20 mm and then 12 hr later to 3 mm to drive off the last traces of alcohol and drive the reactions to completion. In this manner, poly(bithionol sebacate) and poly(bithionol isophthalate) with inherent viscosities of 0.56 and 0.38 dl/g were produced in yields of 94% and 100% respectively.

The poly(bithionol polysebacate) displayed a weak absorbtion in the infrared spectrum at 3075 cm^{-1} corresponding to aromatic C-H stretching and stronger absorbtions at 2930 and 2850 cm^{-1} corresponding to aliphatic C-H stretching. A carbonyl absorbtion at 1775 cm^{-1}, typical of aliphatic/aromatic polyesters, was also observed. The ^{1}H NMR

TABLE 17

PREPARATION OF BITHIONOL POLYESTERS--INFLUENCE OF POLYMERIZATION TECHNIQUE[a]

Polyester	η_{inh}[b] (dl/g)	Polymerization Technique
adipate[c]	0.05	solution
adipate	0.18	interfacial
sebacate[d]	0.56	melt
isophthalate	0.06	solution
isophthalate	insoluble	high temp. solution
isophthalate	0.07	interfacial
isophthalate[d]	0.38	melt

(a) bithionol + acid chloride; quantitative yield

(b) 0.5% in DMAc

(c) 65% yield

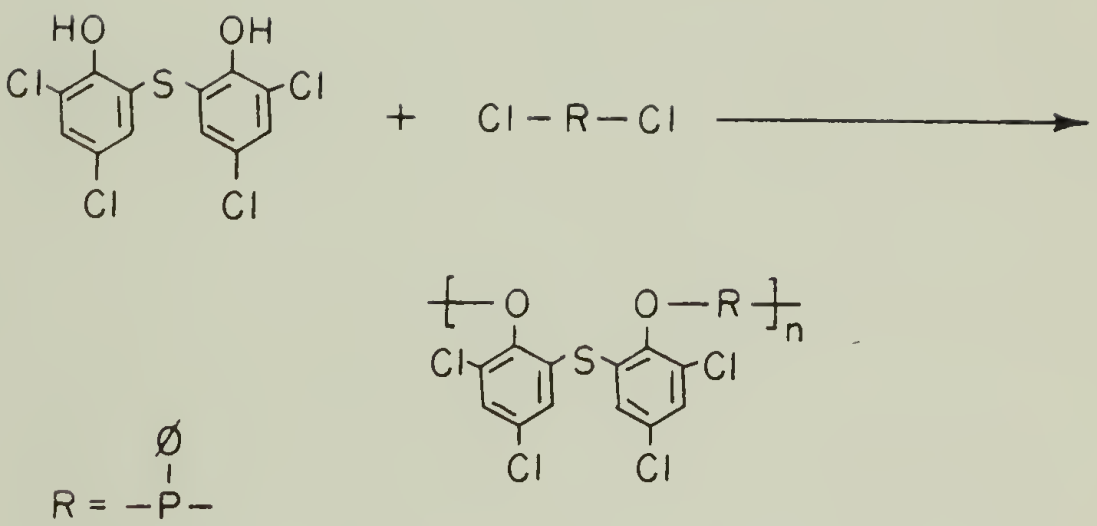
(d) bithionol + dimethyl ester

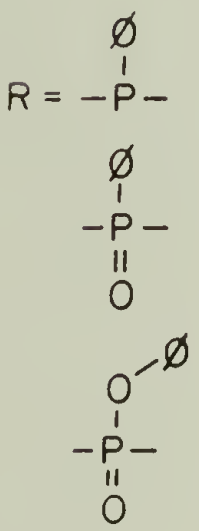
spectrum displayed three multiplets assignable to methylene protons, one centered at δ 1.35 corresponding to internal methylene protons, one centered at δ 1.65 and partially superimposed on the first multiplet corresponding to $\underline{CH}_2\underline{CH}_2\overset{O}{\overset{\|}{C}}\text{-O}$ protons, and one centered at δ 2.6 due to $\underline{CH}_2\overset{O}{\overset{\|}{C}}\text{-O}$ protons. A symmetrical multiplet due to the aromatic protons in the polymer was observed centered around δ 7.3. The ratio of integrated peak areas was consistent with the proposed structure.

The infrared spectrum of poly(bithionol isophthalate) displayed a weak absorbtion at 3070 cm^{-1}, characteristic of aromatic C-H stretching, a strong carbonyl stretching absorbtion at 1760 cm^{-1}, typical of aromatic/aromatic polyesters, and a strong absorbtion in the C-O stretching region at 1195 cm^{-1}. The ^1H NMR spectrum showed an overlapping of multiplets due to aromatic protons from δ 7.0 to 8.3.

K. Preparation of bithionol polymers containing phosphorous. Three polymers containing both bithionol moieties and phosphorous, in the main chain were synthesized as illustrated in Figure 17. The preparations were carried out as melt polycondensations of bithionol with phenyldichlorophosphate, phenylphosphonic dichloride, and dichlorophenylphosphine. The synthetic procedures were relatively straightforward and all preparations were performed

Figure 17. Synthesis of bithionol polymers containing phosphorous.





simultaneously and under identical conditions. The polymerizations were carried out in three test tubes, each tube containing equimolar portions of bithionol bischloroformate and one of the phosphorous dichloride compounds mentioned above. The tubes were heated under nitrogen at 205°C for 6 hr, after which the pressure was lowered to 20 mm where it was held for an additional 12 hr. The reactions were completed by raising the temperature to 235°C while lowering the pressure to 1 mm over a one hour period. During the course of the reactions, some gas bubbles were observed escaping from the increasingly viscious melts. When cooled, all of the polymers formed pale orange glasses, which were dissolved in methylene chloride and precipitated into methanol. Poly(bithionol phenylphosphate) was obtained as a white powder in 76% yield. Its inherent viscosity was found to be 0.19 dl/g. The poly(bithionol phenylphosphonate), on the other hand, was obtained as a beige powder in 57% yield. The inherent viscosity of this material was found to be 0.08 dl/g. The poly(bithionol-phenylphosphinate) was obtained as a tacky orange polymer in 19% yield with an inherent viscosity of 0.16 dl/g. The identity of the polymers was confirmed by infrared and ^{1}H HMR spectra, as well as by microanalysis.

Poly(bithionol phenylphosphate) showed a weak absorbtion in the infrared at 3070 cm^{-1} attributed to C-H stretching, as well as stronger absorbtions corresponding

to aromatic C-C stretching at 1435 cm^{-1}, P=O stretching at 1305 cm^{-1}, and P-O stretching at 1190 cm^{-1}. The ^{1}H NMR showed multiplets due to aromatic protons at δ 7.2-7.7. The multiplets were superimposed on one another, however, making their respective integrations impossible.

The infrared spectrum of poly(bithionol phenylphosphonate) showed a weak absorbtion in the aromatic C-H stretching region at 3060 cm^{-1}, as well as stronger absorbtions in the aromatic C-C and P-O stretching regions at 1430 and 910 cm^{-1}, respectively. The ^{1}H NMR spectrum was similar to that of poly(bithionol phenylphosphate) with differentiation of the aromatic proton multiplets impossible due to significant overlap.

The infrared spectrum of poly(bithionolphenylphosphinate) showed strong phenolic O-H stretching at 3400 and 3340 cm^{-1}. A weak absorbtion at 3070 cm^{-1} and a moderate absorbtion at 1455 cm^{-1} were attributed to aromatic C-H and C-C stretching, respectively. The ^{1}H NMR spectrum showed the expected aromatic proton multiplets centered at δ 7.1 and 7.5. The strong absorbtions in the infrared spectrum at 3400 and 3340 cm^{-1} indicated that the polymer was endcapped with bithionol phenolic groups. The polymer was also found to have a Cl content of 34.10%, an increase of 3.41% over the theoretical content of 30.69% Cl, further evidence of the presence of bithionol endgroups. A degree of polymerization of 8-10 was calculated from the micro-

analytical data.

IV. Preparation of Polymers from Hindered Bisphenols

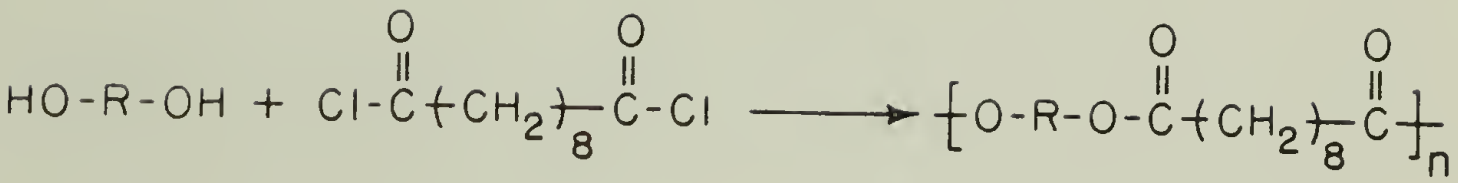
During the course of this research it was found that many of the attempts to produce polymers containing bithionol in the chain backbone resulted in the formation of materials of low to moderate molecular weight. Although high molecular weight polymers were eventually prepared, a number of factors were seen as possibly having contributed to the difficulty with which bithionol could be used as a condensation monomer. First, bithionol is a 2,2'-thiobisphenol. Most bisphenols used for the commercial production of engineering plastics, such as polyesters and polycarbonates, have phenolic hydroxyl groups in the para position. The ortho position of the phenolic hydroxyl groups in bithionol could clearly have had an effect on its chemical behavior and resultant polymerizability. Second, bithionol is sterically hindered, being substituted in all four positions ortho to the phenolic hydroxyl groups. The steric hindrance was expected to have substantially decreased the ease with which bithionol underwent reaction. Thirdly, bithionol is substituted with electron withdrawing chlorine substituents, which makes the bisphenol considerably more acidic than unsubstituted compounds. An increase in acidity usually results in a decrease in the reactivity of

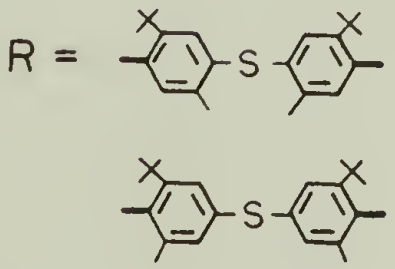
phenolic compounds. Finally, the two phenolic rings in bithionol are connected with a sulfur atom and it was not clear what effect the thio group had on the polymerizability of bithionol.

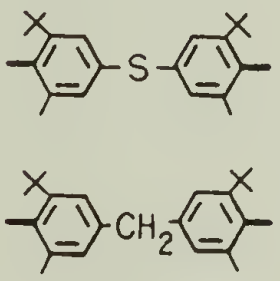
In order to gain further insight into which, if any, of these factors played significant roles in the use of bithionol as a condensation monomer, a series of polymerization reactions were carried out with model compounds (Figure 18). These model compounds were all bisphenols; one was substituted in the 2,2' position, the others were 4,4' substituted bisphenols. Two of the compounds were thiobisphenols and two were methylenebisphenols. All of the compounds were sterically hindered, having methyl and/or tert-butyl substituents ortho to the phenolic hydroxyl groups. The model compounds were condensed with sebacyl chloride in chloroform solution using tributylamine as an acid acceptor. The purity of the solvent, base, and acid chloride were checked by carrying out a test polymerization using 2,2-(4-hydroxyphenyl)propane (bisphenol A) as a comonomer. Polyester with an inherent viscosity of 0.83 dl/g (0.5% in $CHCl_3$) was easily obtained.

The results of the polymerization reactions with the substituted bisphenols are shown in Table 18. It was clear that the position of the linkage of the phenol groups had no effect on the polymerizability of either of the isomeric methylenebisphenols. Both reactions gave polymers

Figure 18. Synthesis of polymers from hindered bisphenols.







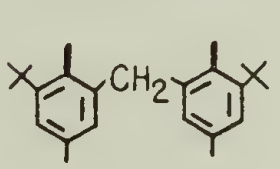
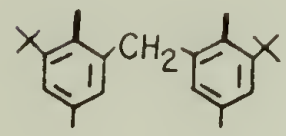
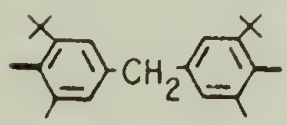
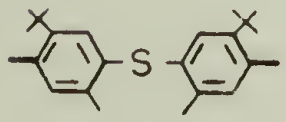
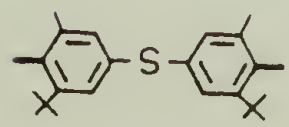


TABLE 18

PREPARATION OF POLYMERS[a] FROM HINDERED BISPHENOLS

Bisphenol	Yield in %	η_{inh}[b] in dl/g
	67	0.23
	77	0.24
	93	0.59
	90	0.65

(a) polysebacate prepared from bisphenol and sebacyl chloride

(b) 0.5% in $CHCl_3$

with nearly identical inherent viscosities and in similar yields. The nature of the group joining the two phenol rings, however, did play a significant role in the outcome of the reaction, as the thiobisphenols produced polymers in higher yields and with higher molecular weights than the methylenebisphenols. It was thus demonstrated that bisphenols with a considerable amount of steric hindrance can still be polymerized to reasonable molecular weight.

These studies seemed to indicate that the inductive effect of the four electron withdrawing chlorine groups and the consequent increase in acidity was primarily responsible for the low molecular weights obtained in several of the reactions involving bithionol. An examination of the literature, however, reveals numerous examples of the polymerization to high molecular weight of halo-substituted bisphenols. Many of these examples were discussed in Chapter I. There is no report in the literature, however, on the use of a tetrachlorosubstituted 2,2'-bisphenol in a condensation polymerization. In light of these results, it seemed that the difficulty in producing high molecular weight polymers from some of the polymerization reactions carried out with bithionol may not have been due to any one of the factors mentioned, but may have actually been the result of a combination of all of them.

V. Measurement of the Rates of Hydrolysis of Bithionol Polymers

In order to determine the suitability of polymers containing pharmacologically active groups in the backbone for use in physiological environments it was necessary to examine the relative hydrolytic stabilities of different types of polymers under conditions resembling those encountered in biological systems. Due to the complexity of living systems and the many variables inherent in them, conditions for the examination of some of the polymers produced in this research were chosen so as to eliminate as many of these variables as possible. A simple aqueous system maintained at a temperature of 37°C and buffered to a pH of 7.4 was used. This system, although providing data not directly comparable to in vivo studies, should provide an indication as to the relative usefulness of bithionol polymers as hydrolyzable drug delivery systems.

The polymers chosen for study were expected to degrade at slow rates under the mild conditions employed. A technique sensitive enough to detect even small amounts of hydrolysis was therefore necessary. Bithionol, a hydrolytic degradation product of all of the polymers studied, absorbs very strongly at 318 nm in the ultraviolet region of the spectrum, allowing it to be detected at concentrations as low as 10^{-6} moles per liter. The increase in concentration of bithionol with time was therefore used as a

measure of the rate of hydrolysis of the polymers. A plot of the absorbtion of ultraviolet light at 318 nm as a function of the concentration of bithionol is shown in Figure 19. It can be seen that the absorbance is linear over the range of concentrations examined, yielding a molar extinction coefficient of 1.58×10^4 liter·mole^{-1}·cm^{-1}.

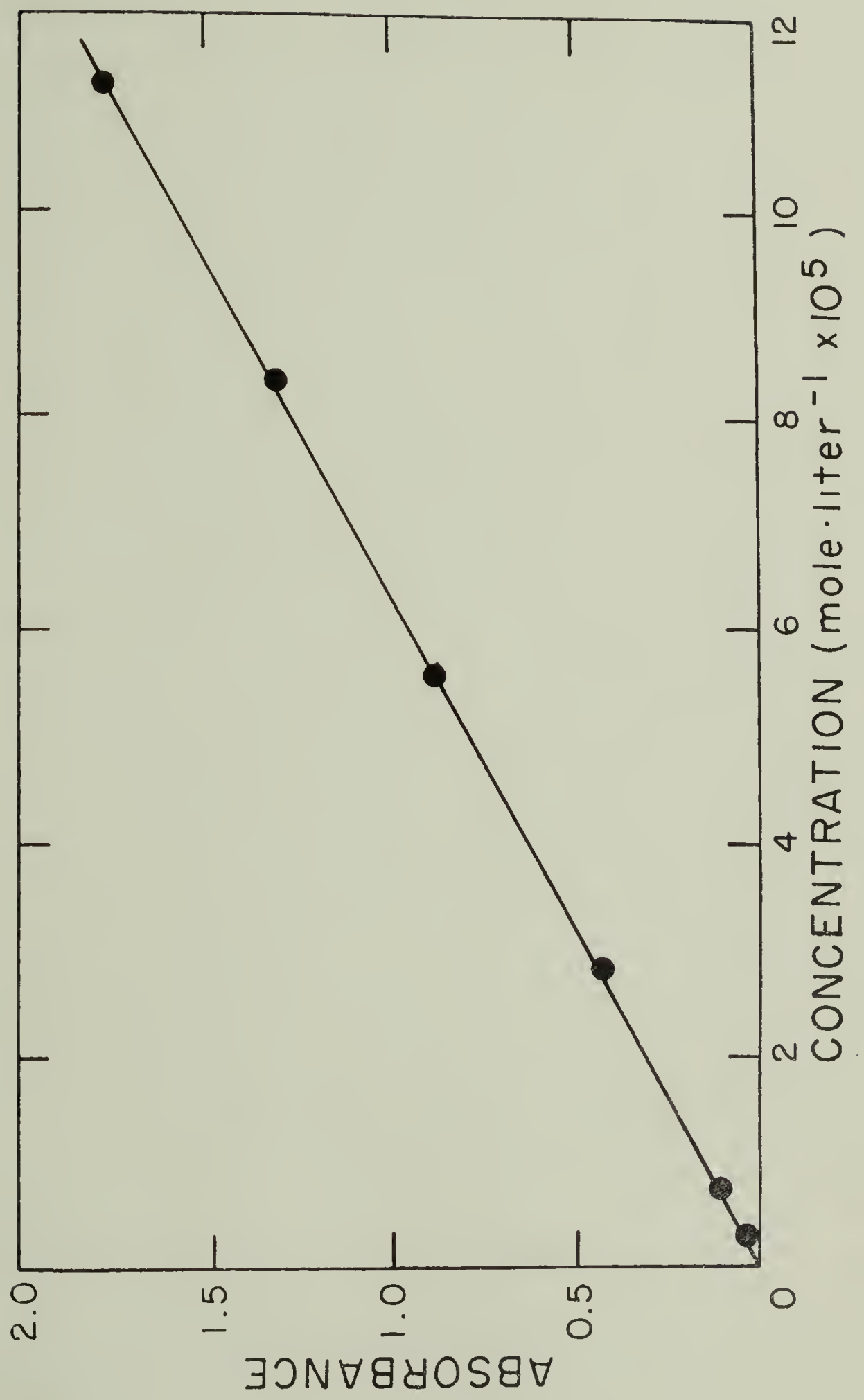
The hydrolysis studies were carried out with appropriately buffered polymer solutions maintained at 37°C in a constant temperature water bath. The mixtures were agitated every 24 hr by bubbling a rapid stream of nitrogen through them. At periodic intervals, aliquots were removed, suitably diluted with pH 10.0 buffer solution, and the absorbance at 318 nm measured. Using the calibration curve obtained earlier, the concentration of bithionol in each of the solutions was calculated using Beer's law:

$$A = \varepsilon bc$$

where A is the absorbance of the solution, ε is the molar extinction coefficient, or molar absorptivity, expressed in liter·mole^{-1}·cm^{-1}, c is the concentration in moles·liter^{-1}, and b is the path length of solution, in this case, 1 cm.

The solubility of the polymers in aqueous environments was also determined. Two of the polymers studied, the bithionol/PEG 4000 alternating copolycarbonate and the terpolycarbonate from 1,10-decanediol and PEG 4000, were

Figure 19. Absorbance of bithionol vs. concentration.


ABSORBANCE
2.0
1.5
1.0
0.5
0
2
4
6
8
10
12
CONCENTRATION (mole·liter⁻¹ x10⁵)

found to be completely water soluble. Three of the polymers, the terpolycarbonate containing resorcinol and PEG 4000, and the two copolyurethanes containing 1,10-decanediamine and m-phenylenediamine, each with PEG 4000, were found to be highly swellable in water, becoming nearly transparent in the swollen state. All of the remaining polymers were found to be water insoluble.

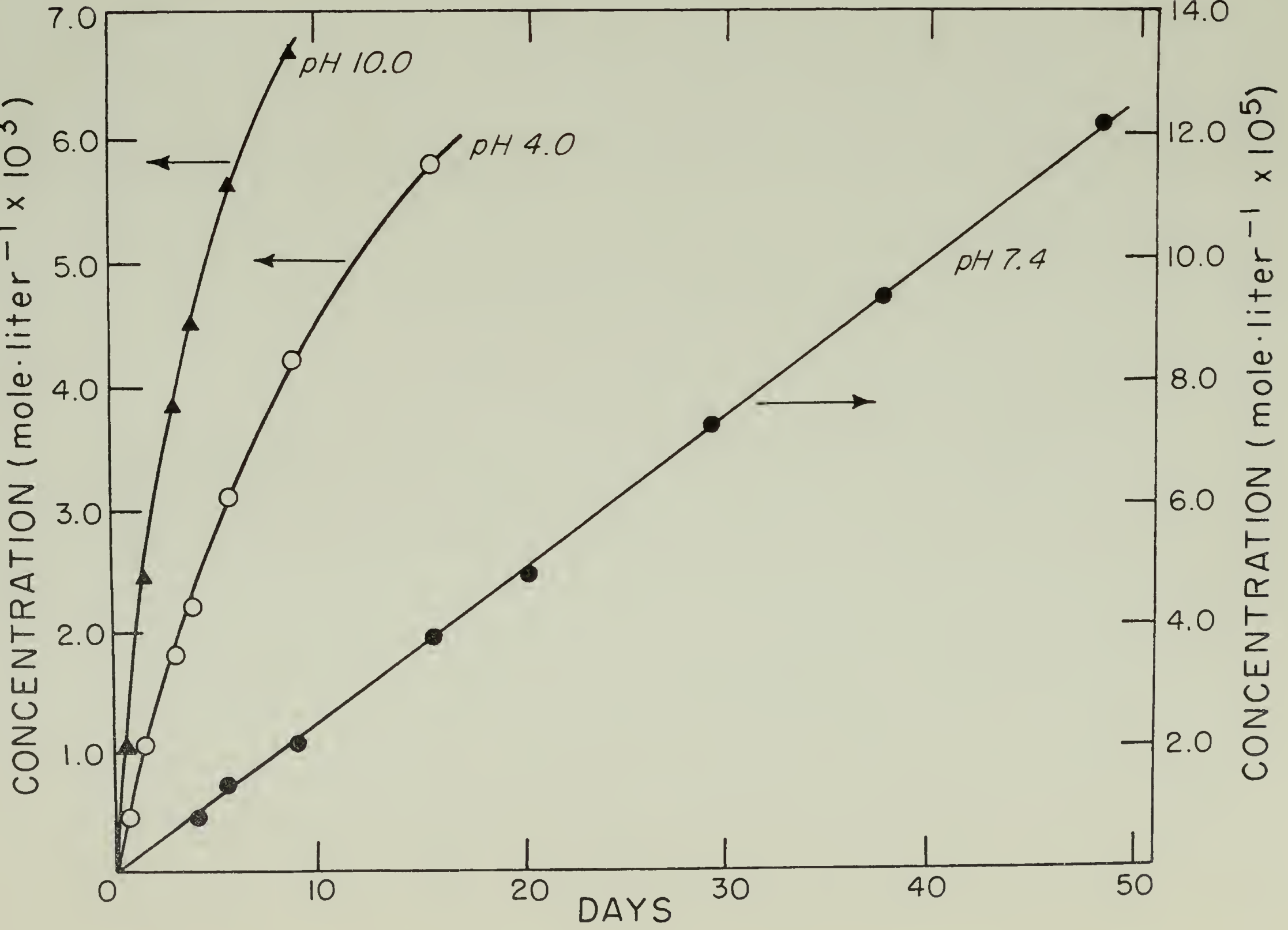
In addition to the hydrolysis studies carried out at pH 7.4, the water soluble bithionol/PEG 4000 alternating copolycarbonate was also studied at pH's of 4.0 and 10.0. The calculated quantity of bithionol released from the bithionol/PEG 4000 alternating copolymer as a function of time is shown in Figure 20. As expected, the hydrolysis took place more rapidly under acidic and alkaline conditions than it did at a pH of 7.4. The rate of release of bithionol can be seen to decrease with time, indicating non-zero order reaction kinetics. Assuming second order kinetics, rate constants for the hydrolyses can be obtained using the following kinetic equation developed by Szabó-Rethy and Vancsó-Szmercsányi:[72]

$$\ln \frac{E_o}{E_o - x} = kct$$

where E_o = initial concentration of ester or urethane groups in mole·liter^{-1},

x = concentration of bithionol produced by the hydrolysis during a period of t days in moles·liter^{-1},

Figure 20. Concentration of bithionol released from bithionol/PEG 4000 alternating copolycarbonate vs. time.


pH 10.0
pH 4.0
pH 7.4
CONCENTRATION (mole·liter⁻¹ x 10³)
CONCENTRATION (mole·liter⁻¹ x 10⁵)
DAYS
0
10
20
30
40
50
1.0
2.0
3.0
4.0
5.0
6.0
7.0
2.0
4.0
6.0
8.0
10.0
12.0
14.0

k = rate constant of the reaction in liter·mole^{-1}. day^{-1}, and

c = concentration of catalyst in mole·liter^{-1}.

The concentration of hydrolyzable linkages present, Eo, was found to be 4.0 x 10^{-2} mole·liter^{-1} for the samples studied at pH 7.4, and 7.6 x 10^{-3} mole·liter^{-1} for the samples studied at pH 4.0 and 10.0. The concentration of catalyst, c, was assumed to be the concentration of H^+ or OH^- present in the buffered solutions, that is, 10^{-4} mole·liter^{-1} at pH 4.0 and 10.0 and 2.5 x 10^{-7} mole·liter^{-1} at pH 7.4. The validity of the assumption was verified by the experimental results shown graphically in Figure 21. The calculated second order rate constants are shown in Table 19.

TABLE 19

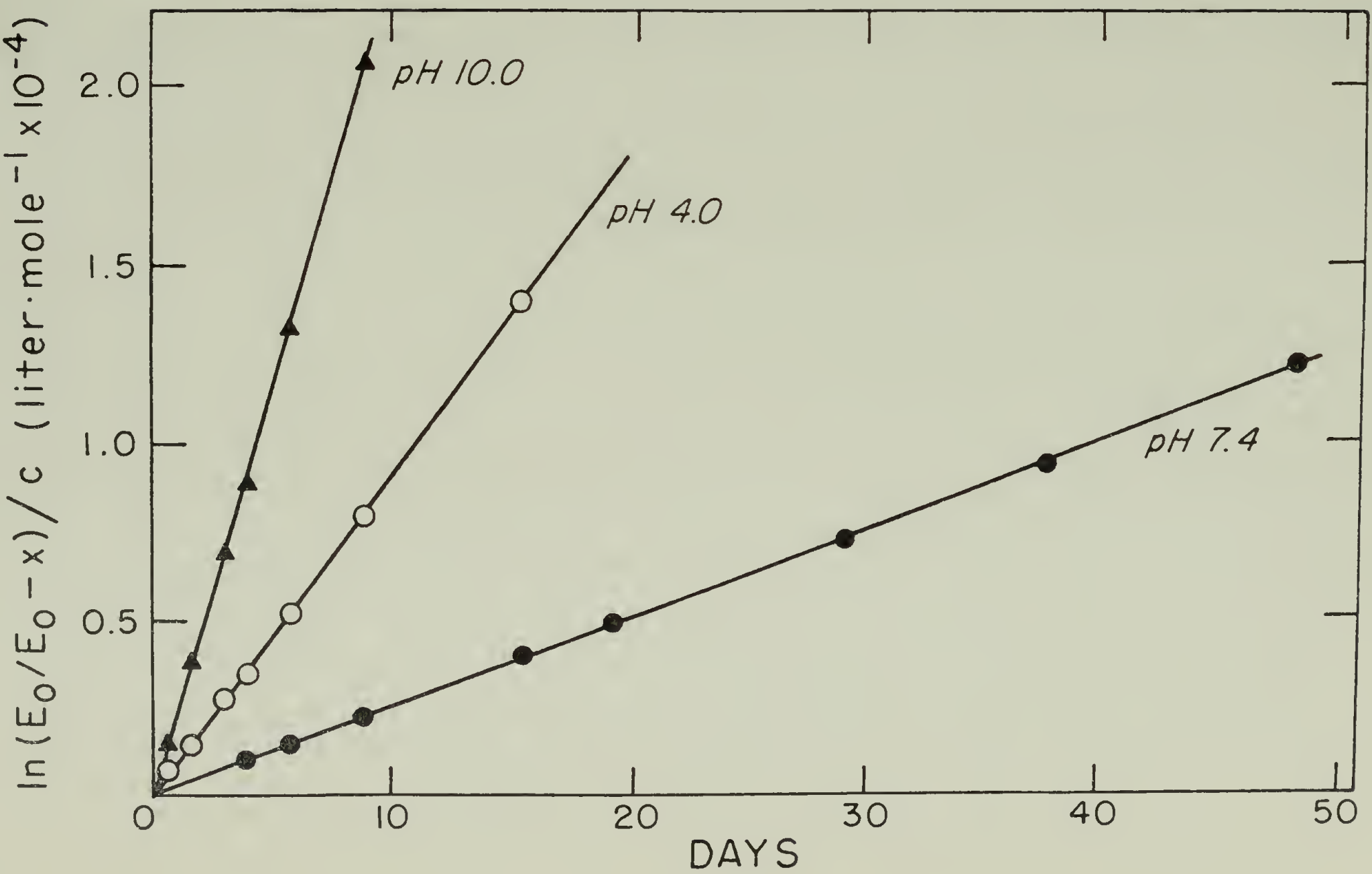
EFFECT OF pH ON THE RATE CONSTANT OF THE HYDROLYSIS OF BITHIONOL/PEG 4000 ALTERNATING COPOLYCARBONATE IN AQUEOUS SOLUTION AT 37°C

pH	k (liter·mole^{-1}·min^{-1})
4.0	0.626
7.4	0.173
10.0	1.625

It can be seen that the polycarbonate was hydrolyzed almost 10 times as fast at pH 10 as it was under neutral conditions, while the hydrolysis at pH 4 was over two times as rapid.

Both the water soluble and the water swellable

Figure 21. $[\ln(E_o/E_{o-x})]/c$ vs. time for bithionol/PEG 4000 alternating copolycarbonate.


pH 10.0
pH 4.0
pH 7.4
2.0
1.5
1.0
0.5
0
10
20
30
40
50
DAYS
ln (E0/E0−x)/c (liter·mole−1 x 10−4)

polymers showed similar kinetic behavior in neutral solution as shown in Figures 22 and 23. The calculated rate constants are compared in Table 20.

TABLE 20

RATE CONSTANTS OF THE HYDROLYSIS OF WATER SOLUBLE POLYMERS IN AQUEOUS SOLUTION AT 37°C; pH 7.4

Polymer	$k \cdot 10^2$ (liter·mole^{-1}·min^{-1})	Relative amount of PEG 4000 as comonomer (%)
Bithionol/PEG 4000 alternating copolycarbonate	17.3	100
Bithionol/1,10-decanediol/ PEG 4000 terpolycarbonate	13.3	93
Bithionol/resorcinol/PEG 4000 terpolycarbonate(a)	4.7	30
Bithionol/1,10-decanediamine/ PEG 4000 copolyurethane(a)	3.5	22
Bithionol/m-phenylenediamine/ PEG 4000 copolyurethane(a)	4.0	25

(a) water swellable

Although significant differences can be seen between the rate constants of hydrolysis for the polymers containing different comonomers, the content of PEG 4000 seems to have had profound influence on the rate of hydrolysis. This phenomenon is similar to that observed in 1972 by Szabó-Rethy and Vancsó-Szmercsányi[72] who found that although the rate of hydrolysis of polyesters obtained from aliphatic saturated dicarboxylic acids was independent of the chain

Figure 22. Concentration of bithionol released from water soluble and swellable bithionol polymers vs. time.

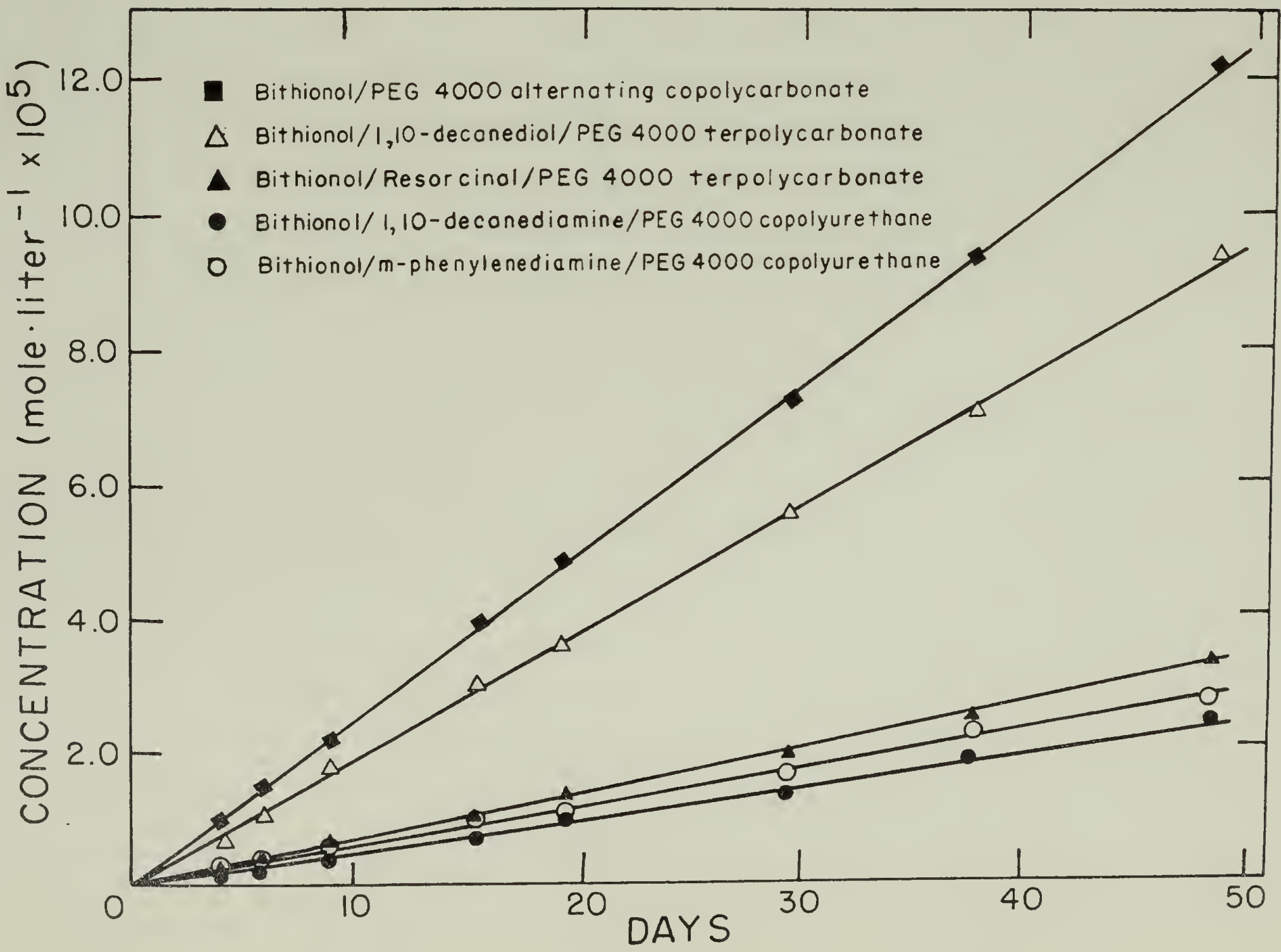
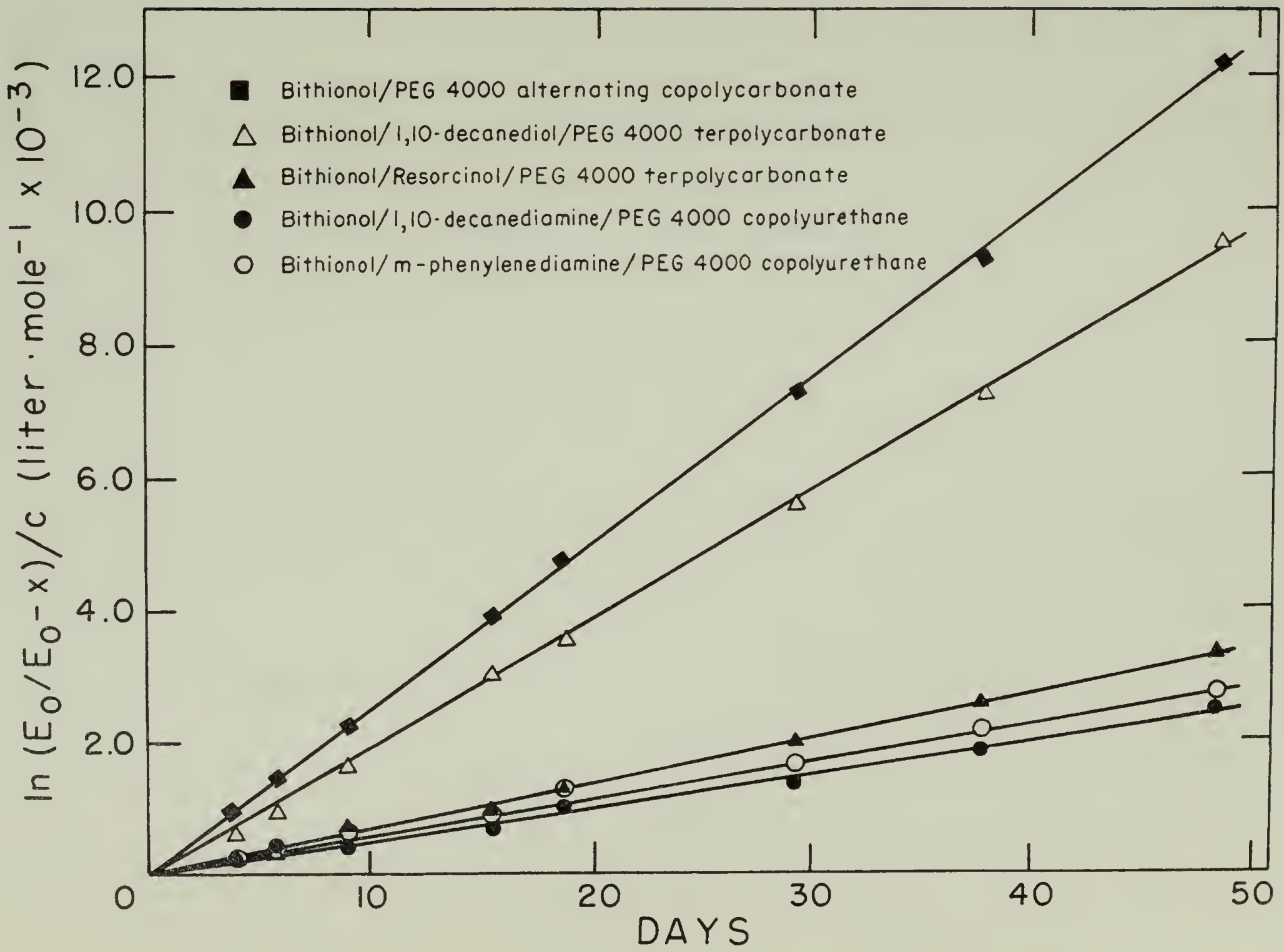

Bithionol/PEG 4000 alternating copolycarbonate
Bithionol/1,10-decanediol/PEG 4000 terpolycarbonate
Bithionol/Resorcinol/PEG 4000 terpolycarbonate
Bithionol/1,10-decanediamine/PEG 4000 copolyurethane
Bithionol/m-phenylenediamine/PEG 4000 copolyurethane
CONCENTRATION (mole·liter⁻¹ x 10⁵)
12.0
10.0
8.0
6.0
4.0
2.0
0
10
20
30
40
50
DAYS

Figure 23. $[\ln(E_o/E_{o-x})]/c$ vs. time for water soluble and swellable bithionol polymers.


Bithionol/PEG 4000 alternating copolycarbonate
Bithionol/1,10-decanediol/PEG 4000 terpolycarbonate
Bithionol/Resorcinol/PEG 4000 terpolycarbonate
Bithionol/1,10-decanediamine/PEG 4000 copolyurethane
Bithionol/m-phenylenediamine/PEG 4000 copolyurethane
ln (E0/E0-x)/c (liter·mole-1 x 10-3)
12.0
10.0
8.0
6.0
4.0
2.0
0
10
20
30
40
50
DAYS

length of the acid, the structure of the glycol had a considerable effect on the rate. They noted that ether oxygen atoms in polyesters from diethylene glycol enhanced the rate of hydrolysis by a factor of nearly 2 over that of polyesters prepared from ethylene glycol.

All the other polymers studied were water insoluble. This excluded the possibility of hydrolysis in solution, and consequently limited the hydrolysis to the surface of the polymers where degradation proceeded very slowly. The rates of hydrolysis could be expected to be proportional to the surface area of the polymers, however, the relative amount of surface area present in each of the samples could not be determined. Nevertheless, the increase in concentration of bithionol in the supernatant aqueous solutions was measurable using the technique described above, the errors associated with these measurements made a relative comparison unreliable. The rates of the hydrolysis reactions were estimated, however, using the method of Rudakova et al.,[69] who investigated the kinetics of hydrolysis of insoluble poly(ethylene terephthalate) in aqueous potassium hydroxide solutions. The effective rate constants for the accumulation of monomer in solution were calculated using the following equation:

$$k = \frac{dA}{dt} \cdot \frac{V}{\varepsilon \ell} ,$$

where V is the volume of solution, A and ε are the absorb-

ance and molar extinction coefficient of the monomer species, respectively, and ℓ is the path length, or cell thickness. The reaction rate constant is expressed in units of moles per unit time. Using this equation, the rate constants for the hydrolysis of the water insoluble polymers were calculated and are shown in Table 21. The rates were very slow, and the hydrolysis reactions seemed to be proceeding according to zero-order kinetics. This is reasonable if one considers an expression describing the rate of reaction as:

$$\text{Rate} = \frac{d[A]}{dt} = k[\text{Polymer}]\ [H_2O]$$

where d[A]/dt is the concentration of monomer released per unit time, measured spectrophotometrically, k is the reaction rate constant, and [Polymer] and $[H_2O]$ are the concentrations of polymer and water, respectively. Since water was present in great excess, its concentration was essentially constant. Due to the fact that the degradation of the polymer proceeded at a slow rate, its concentration could also be considered to be constant with time. Combining these quantities into k, the rate of hydrolysis is seen to be independent of concentration, that is, it exhibits zero order kinetics.

As discussed in Chapter I, the presence of divalent metals ions, Mg^{2+} in particular, has a great influence on a number of reactions involving phosphates and phosphate

TABLE 21

REACTION RATE CONSTANTS OF THE HYDROLYSIS OF WATER INSOLUBLE BITHIONOL POLYMERS; 37°C, pH 7.4

Polymer	$k \times 10^{12}$ (mole·min^{-1})
Bithionol polycarbonate	2
Bithionol/1,10-decanediol alternating copolycarbonate	16
Bithionol/resorcinol alternating copolycarbonate	13
Bithionol/1,10-decanediamine alternating copolyurethane	9
Bithionol/m-phenylenediamine alternating copolyurethane	15
Poly(bithionol sebacate)	2
Poly(bithionol isiphthalate)	1
Poly(bithionol phenylphosphate)	5
Poly(bithionol phenylphosphonate)	2
Poly(bithionol phenylphosphinate)	2

esters. Consequently, the effect of 0.001 molar concentration of Mg^{2+} (approximately that encountered in physiological systems) on the rate of hydrolysis of bithionol polymers containing phosphorous in the backbone was investigated. Magnesium, in the form of $MgSO_4$, was added to solutions containing poly(bithionol phenylphosphate), poly(bithionol phenylphosphonate), and poly(bithionol phenylphosphinate), where the effect on the rates of hydrolysis was found to be negligible (Table 22).

TABLE 22

EFFECT OF ADDED Mg^{2+} ON THE RATE CONSTANTS OF THE HYDROLYSIS OF BITHIONOL POLYMERS CONTAINING PHOSPHOROUS; 37°C, pH 7.4

Polymer	$k \times 10^{12}$ (mole·min^{-1})
Poly(bithionol phenylphosphate)	5
Poly(bithionol phenylphosphonate)	2
Poly(bithionol phenylphosphinate)	2
Poly(bithionol phenylphosphate) + 0.001 M Mg^{2+}	7
Poly(bithionol phenylphosphonate) + 0.001 M Mg^{2+}	2
Poly(bithionol phenylphosphinate) + 0.001 M Mg^{2+}	2

VI. Conclusions and Further Work

The objective of this research was two-fold. The

first was to synthesize several novel polymers containing selected monomers with known pharmaceutical activity as integral parts of the chain backbones. The synthetic objectives were successfully completed. Primaquine, one of the drugs used, was found to be difficult to incorporate into the backbone of a polymer chain. This was shown to be due to an unequal reactivity between the primary aliphatic and the hindered secondary aromatic amino groups. Side reactions associated with the quinoline moiety were also shown to be a source of problems. Primaquine was finally incorporated into several polymers of moderate molecular weight by forming biuret linkages with the primary amino group. Bithionol, another biologically active compound, was successfully incorporated into a variety of polyesters including those derived from phosphoric, phosphonic, and phosphinic acids. A number of polycarbonates and polyurethanes were also prepared from the bischloroformate derivative of bithionol.

The second objective of the project was to determine if, in fact, polymers containing labile linkages would undergo hydrolysis under conditions resembling those encountered in a physiological environment, and if so, what factors affected this degradation and the consequent release of these biologically active agents. This objective was also successfully completed. The most important factor that influenced the rate of hydrolysis of the polymer was found

to be solubility. As expected, the polymers that were water soluble or at least swellable were found to hydrolyze at a rate many times faster than polymers that were insoluble. The presence of hydrophilic polyoxyethylene segments were also found to enhance the rate of hydrolysis.

Although a number of different types of polymers containing bithionol were prepared and their hydrolytic stability under mild aqueous conditions studied, the actual biological activity of all of the polymers prepared in this study should also be investigated. Particular emphasis should be placed on the effect of factors such as crystallinity, copolymer composition, hydrophilicity and hydrophobicity, molecular weight, and solubility.

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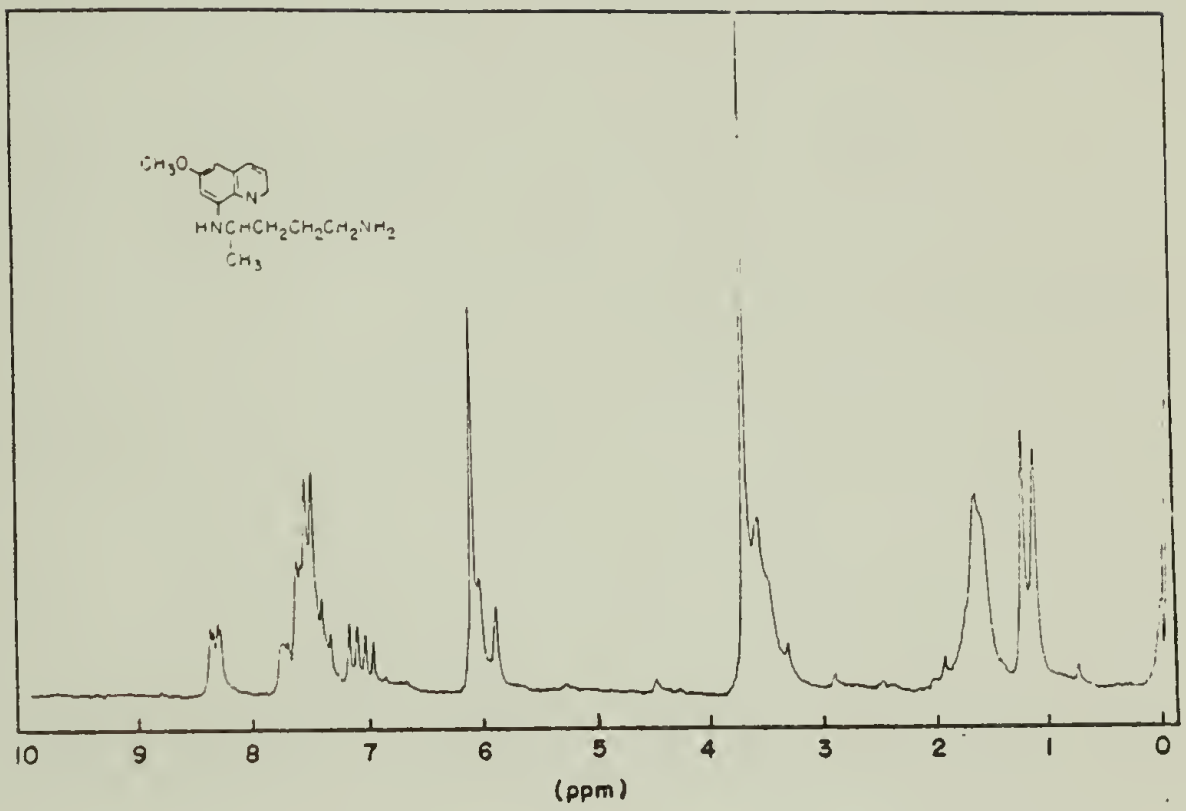
A P P E N D I X A

PROTON MAGNETIC RESONANCE SPECTRA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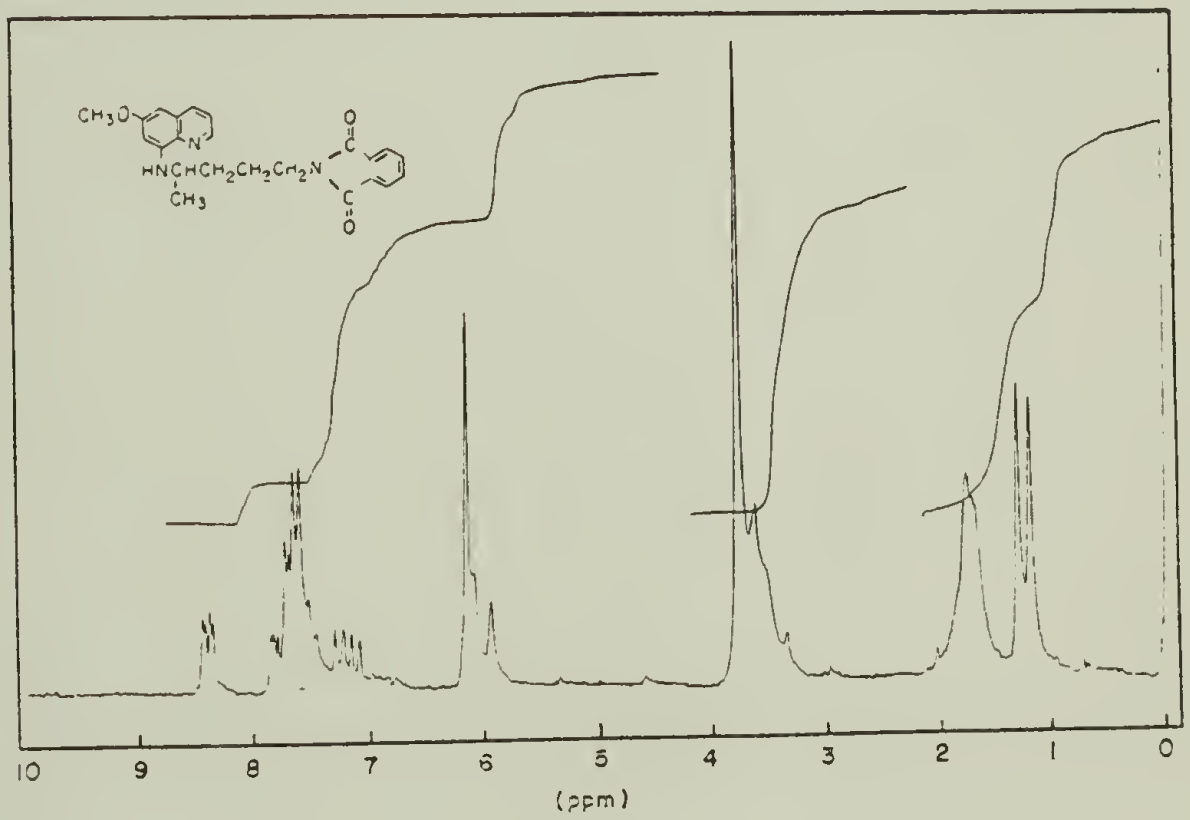
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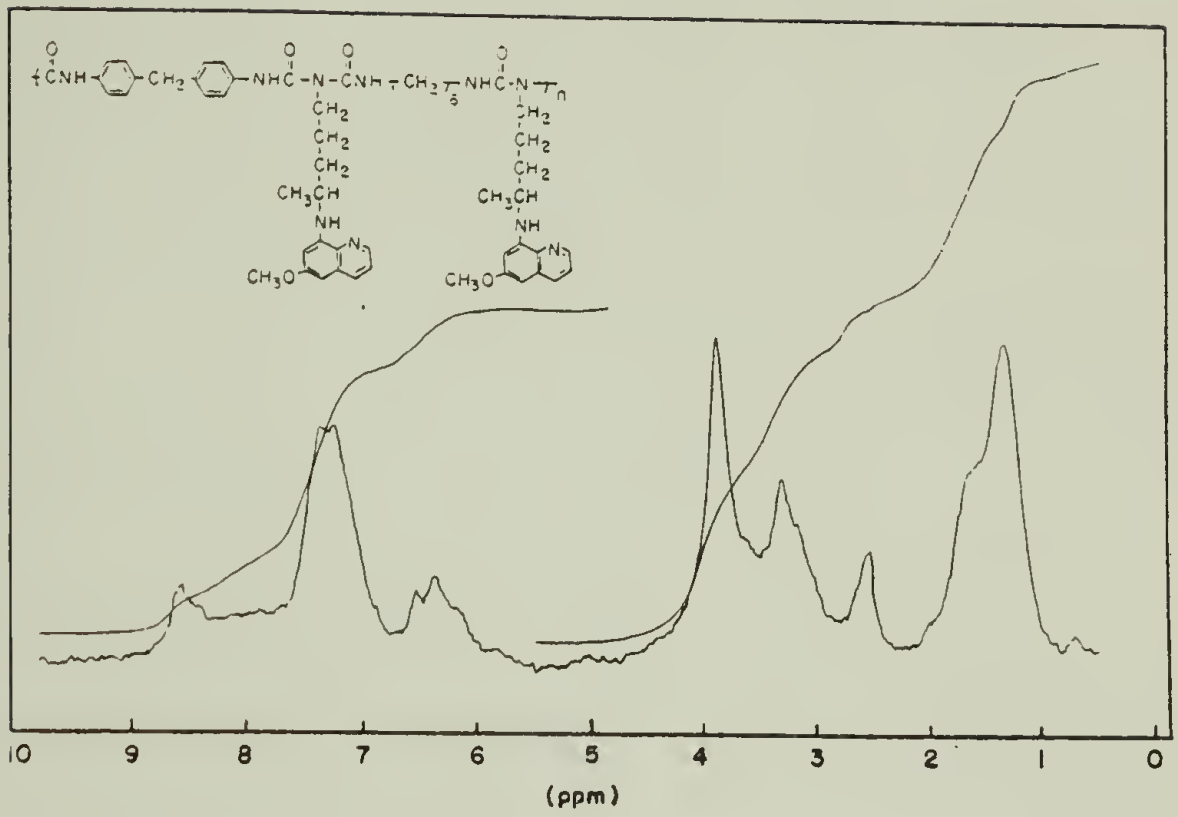
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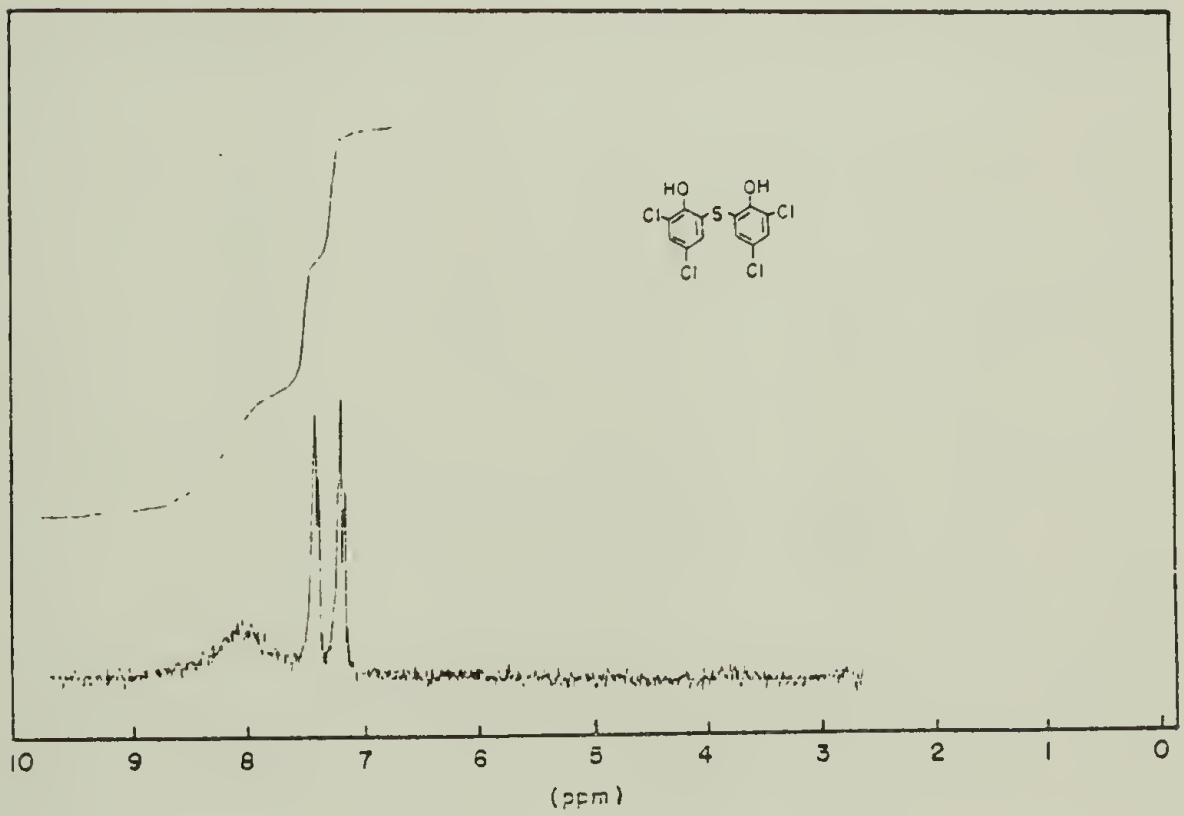
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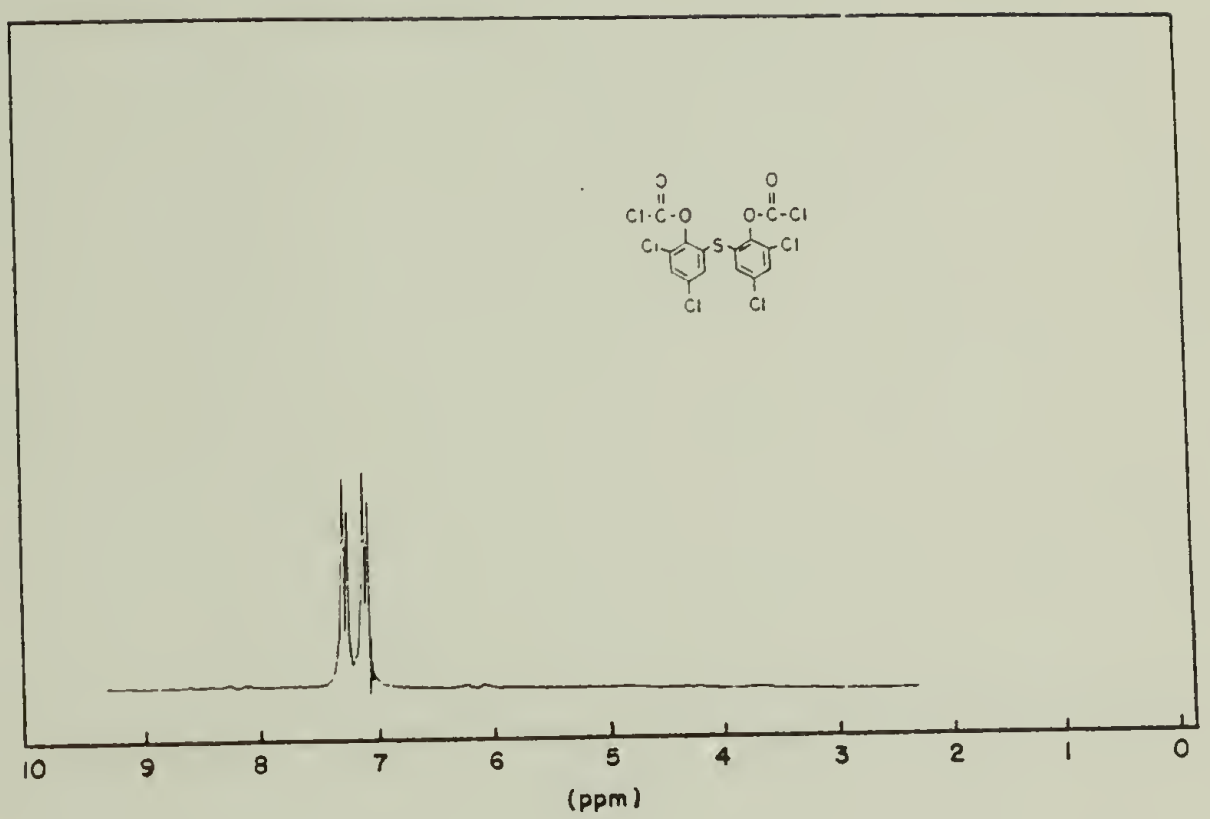
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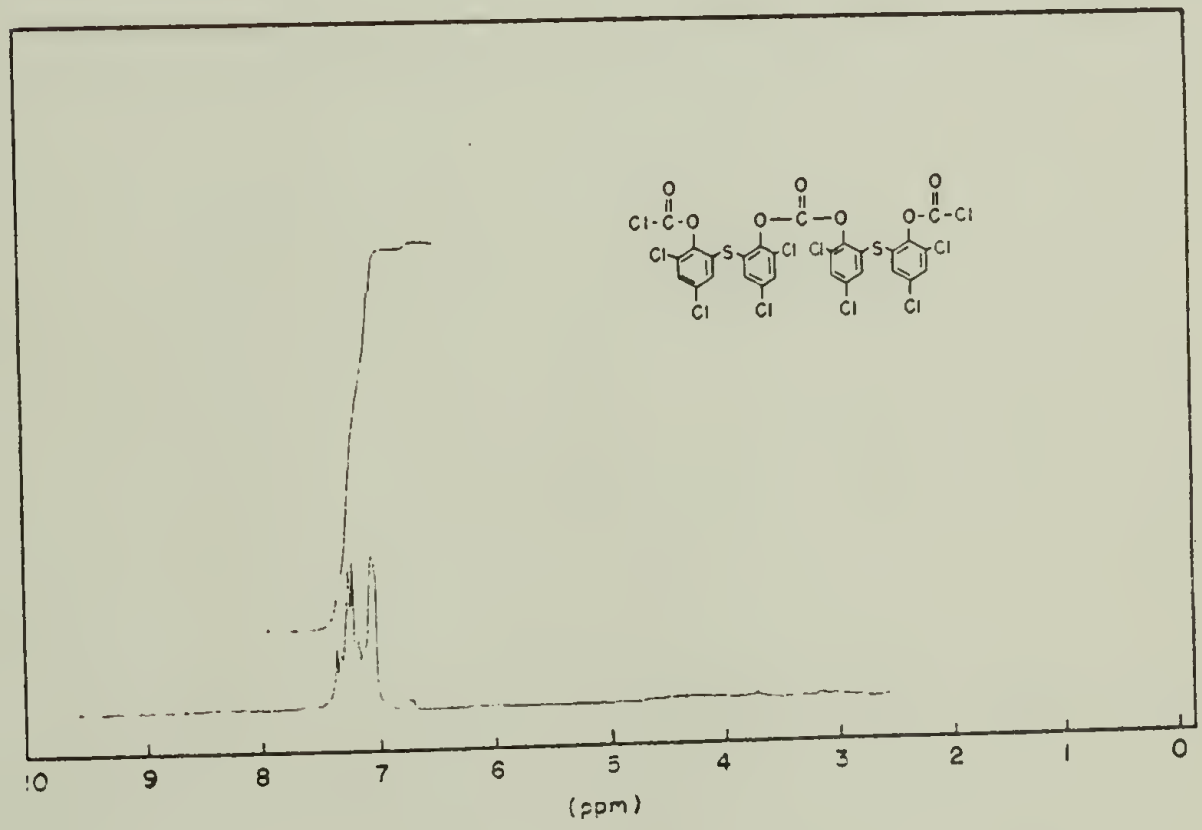
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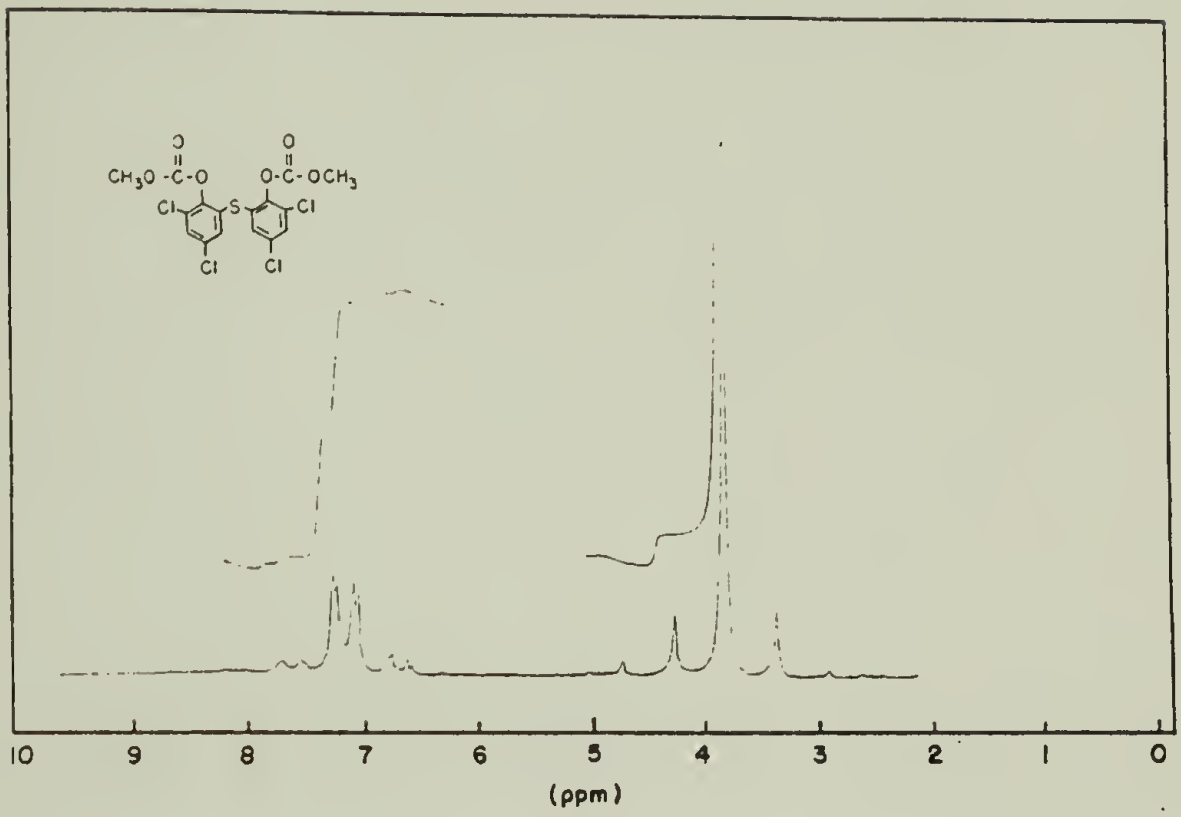
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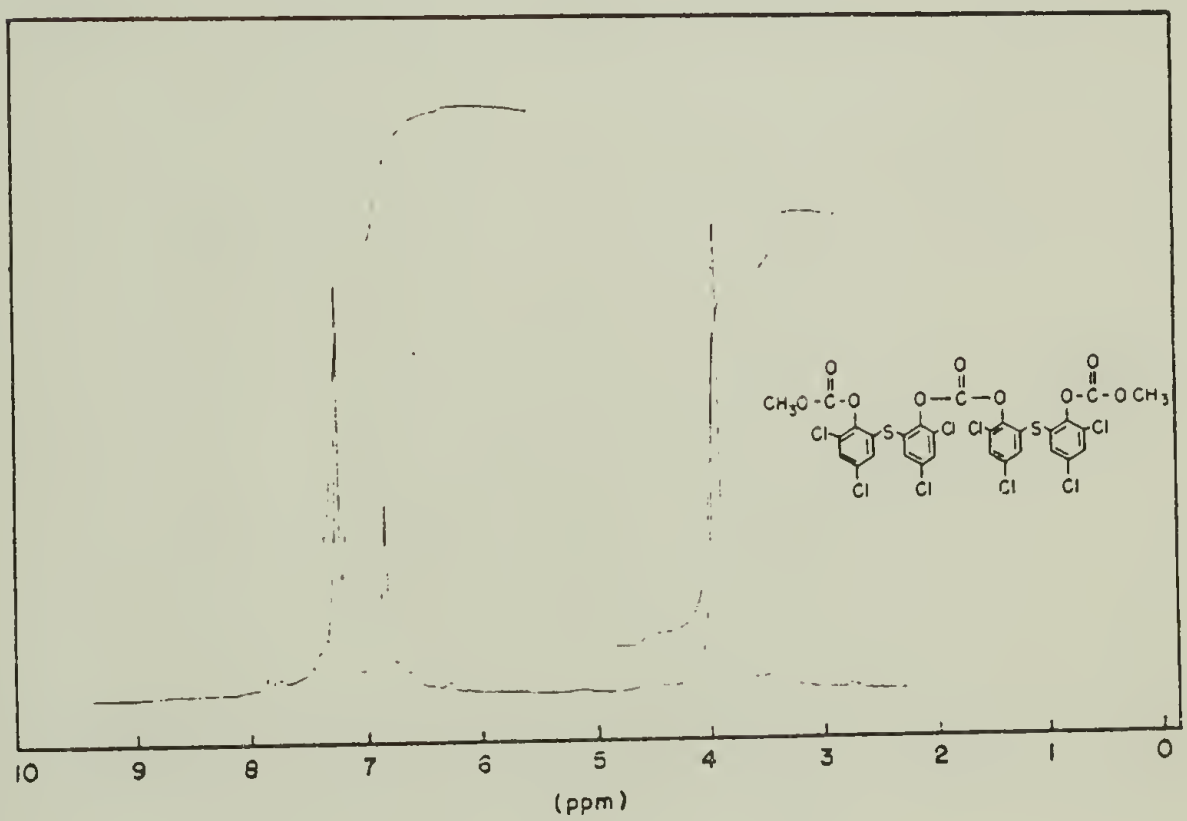
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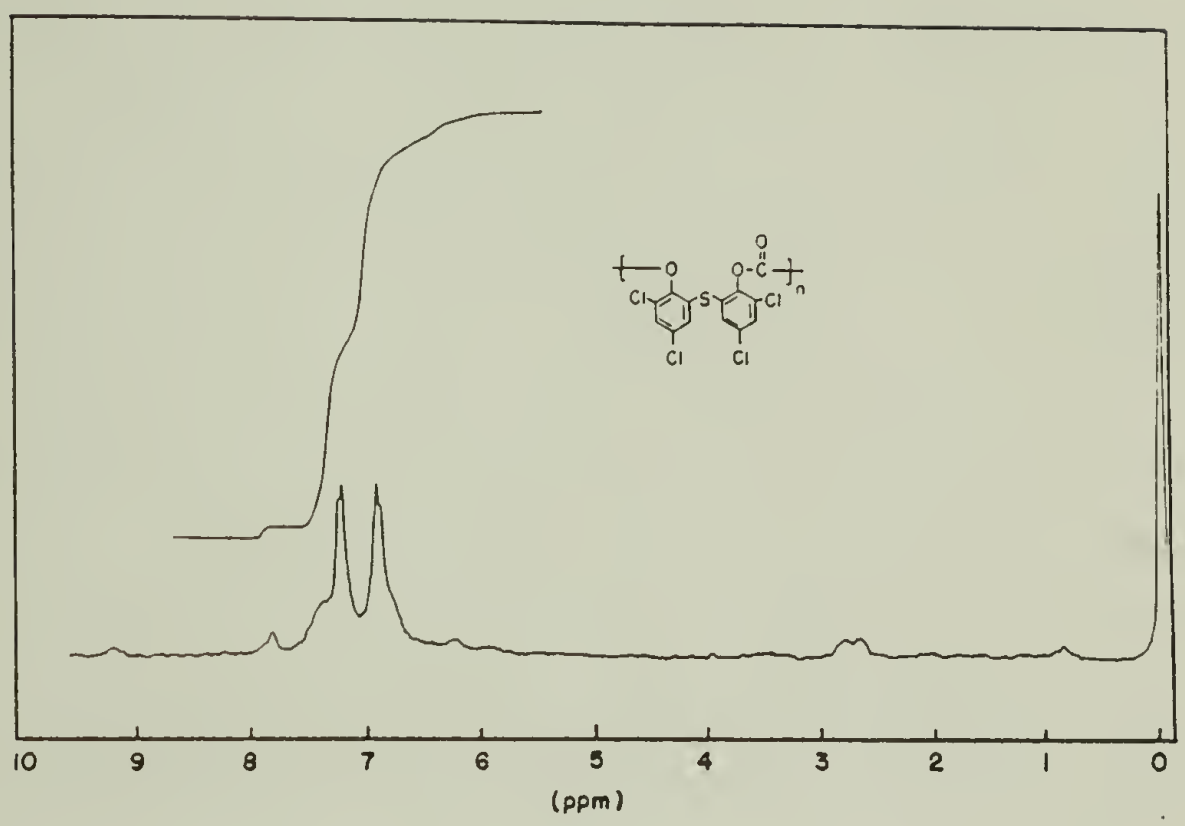
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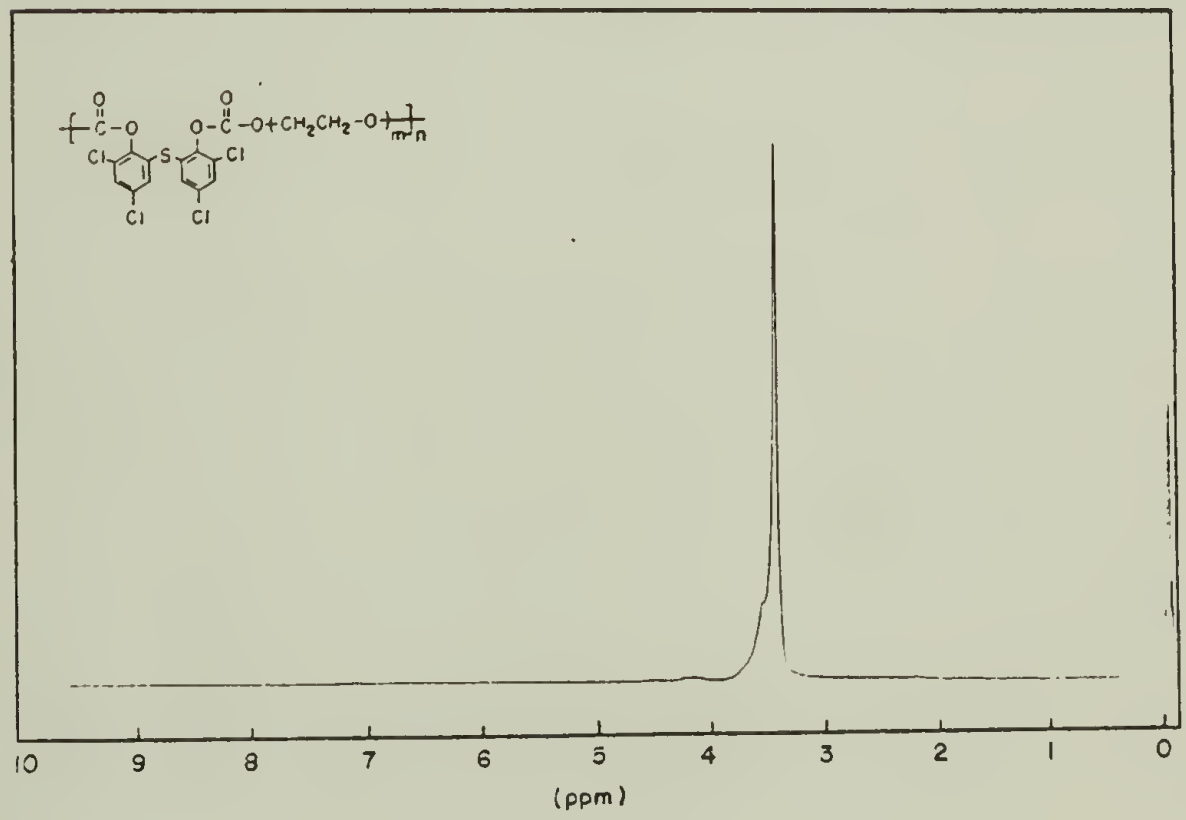
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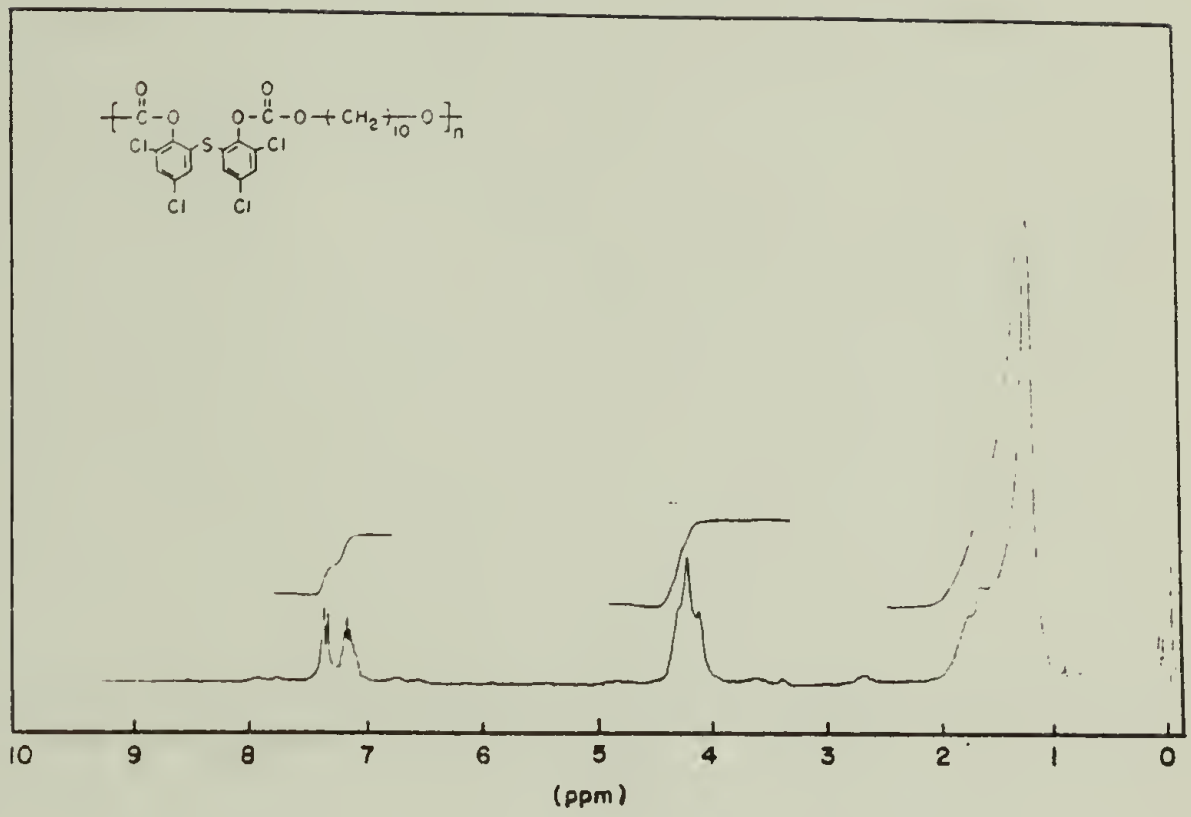
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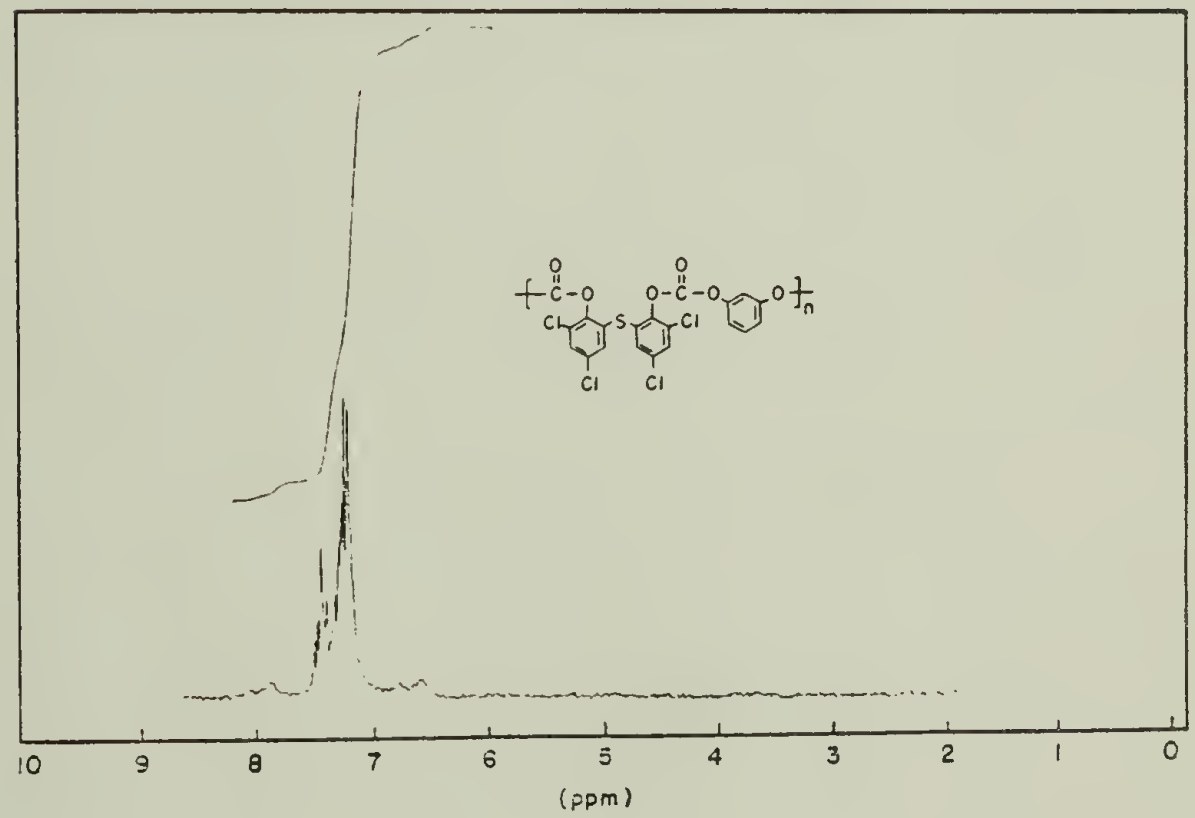
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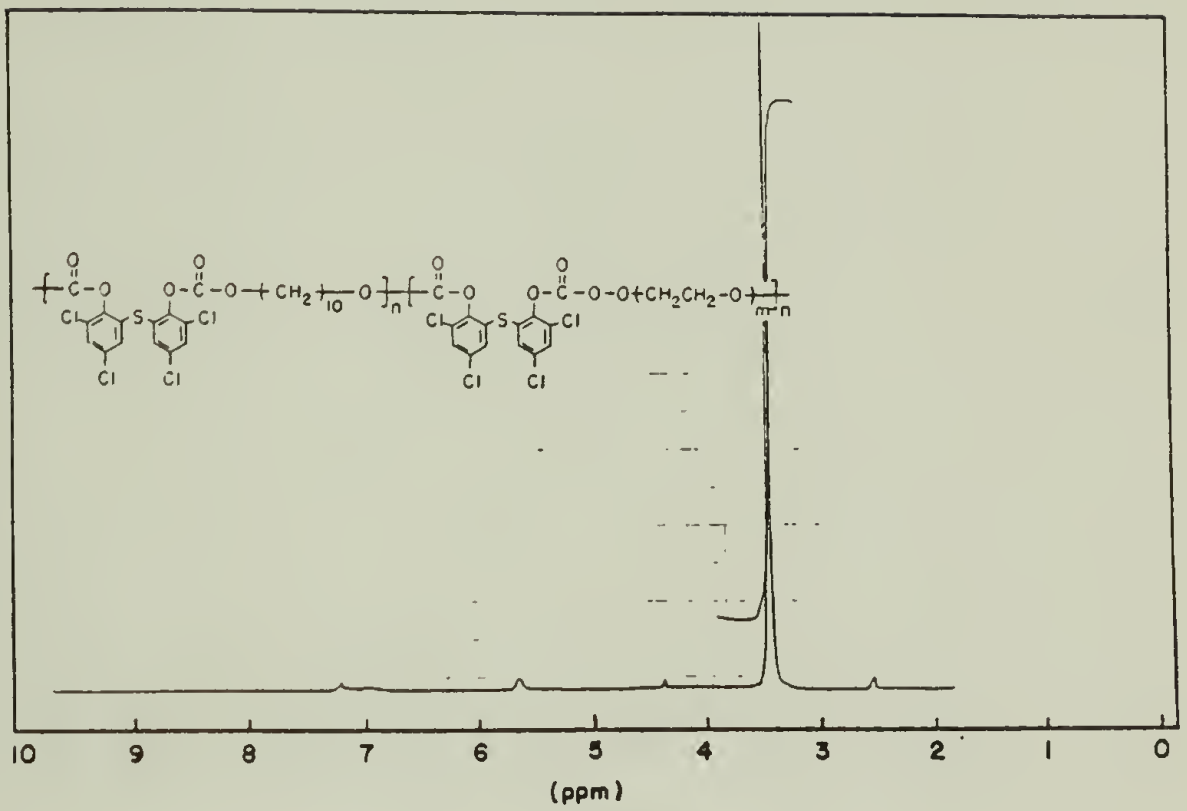
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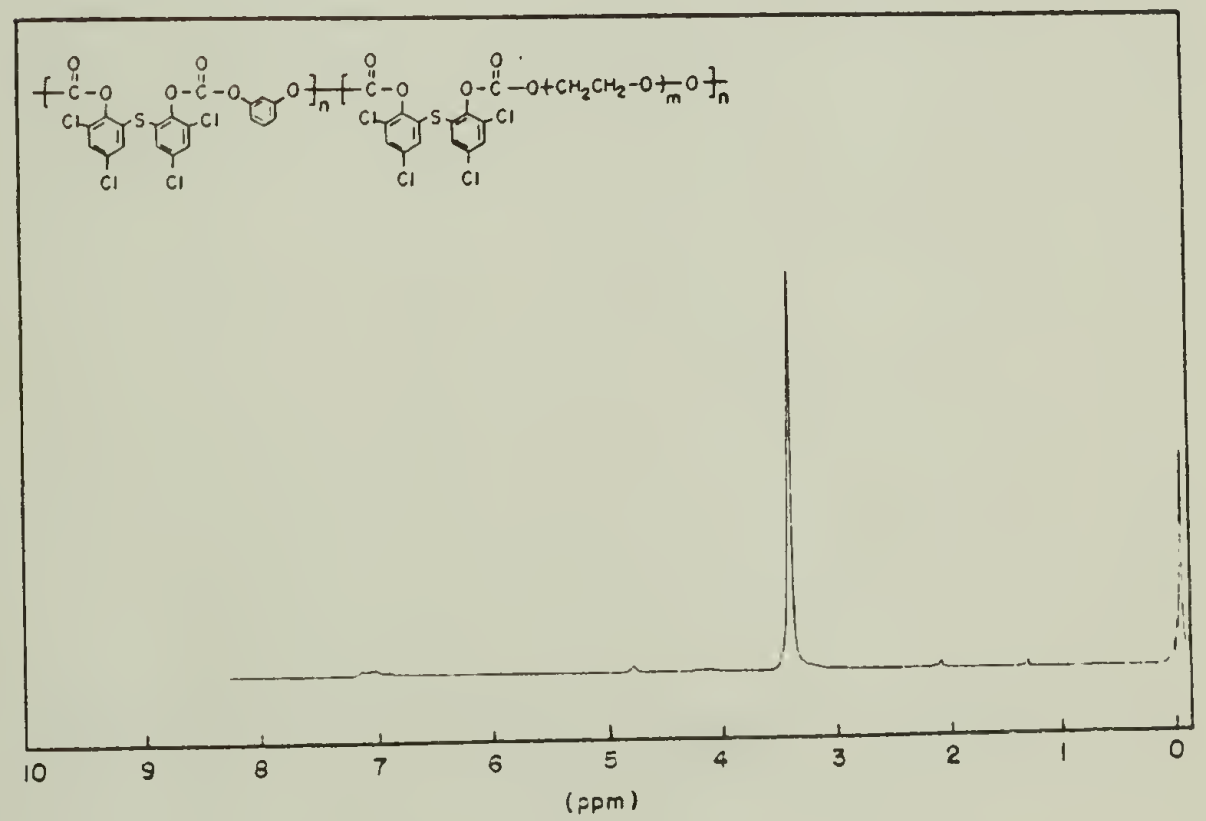
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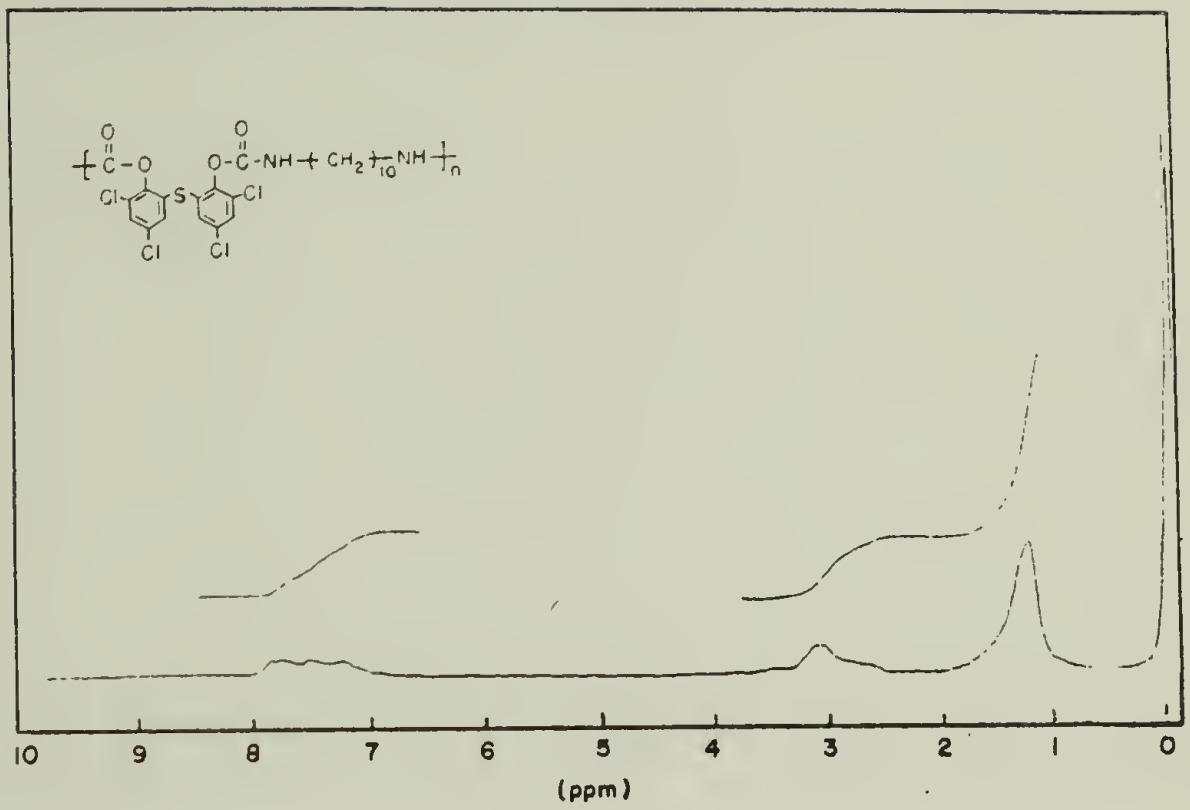
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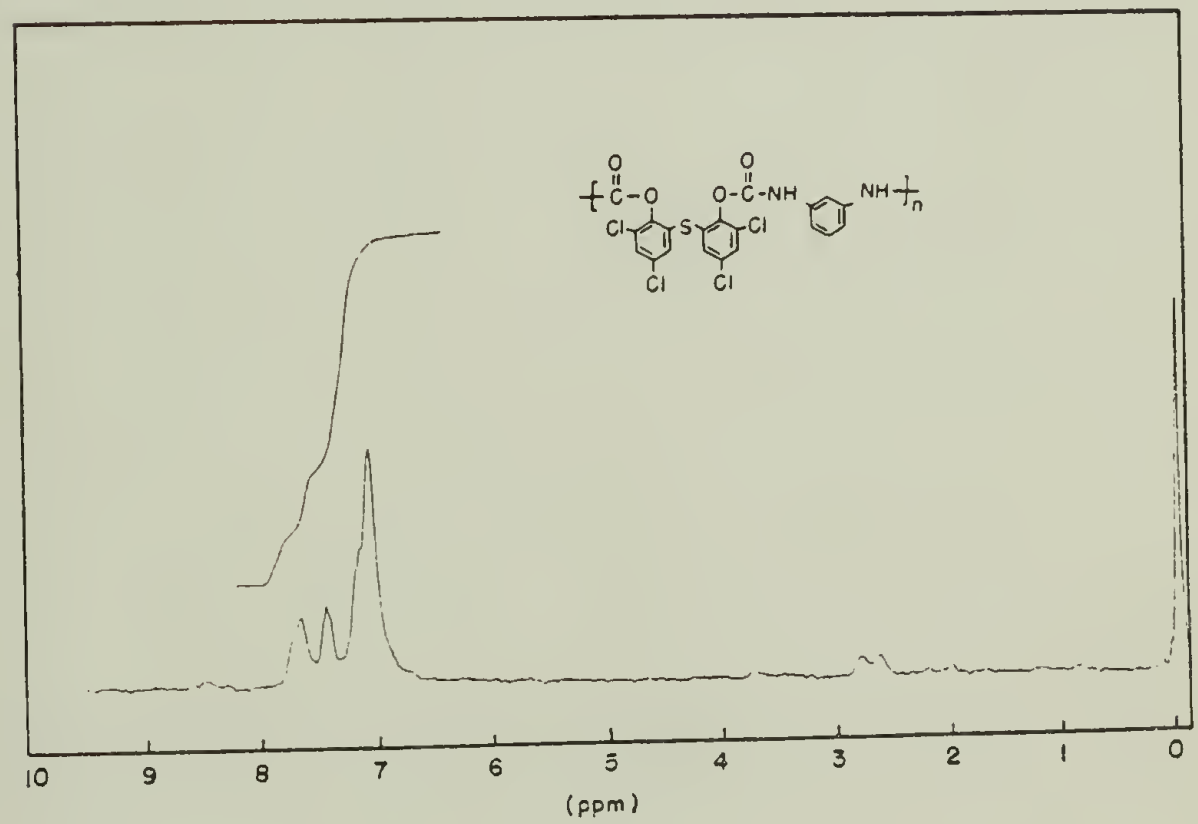
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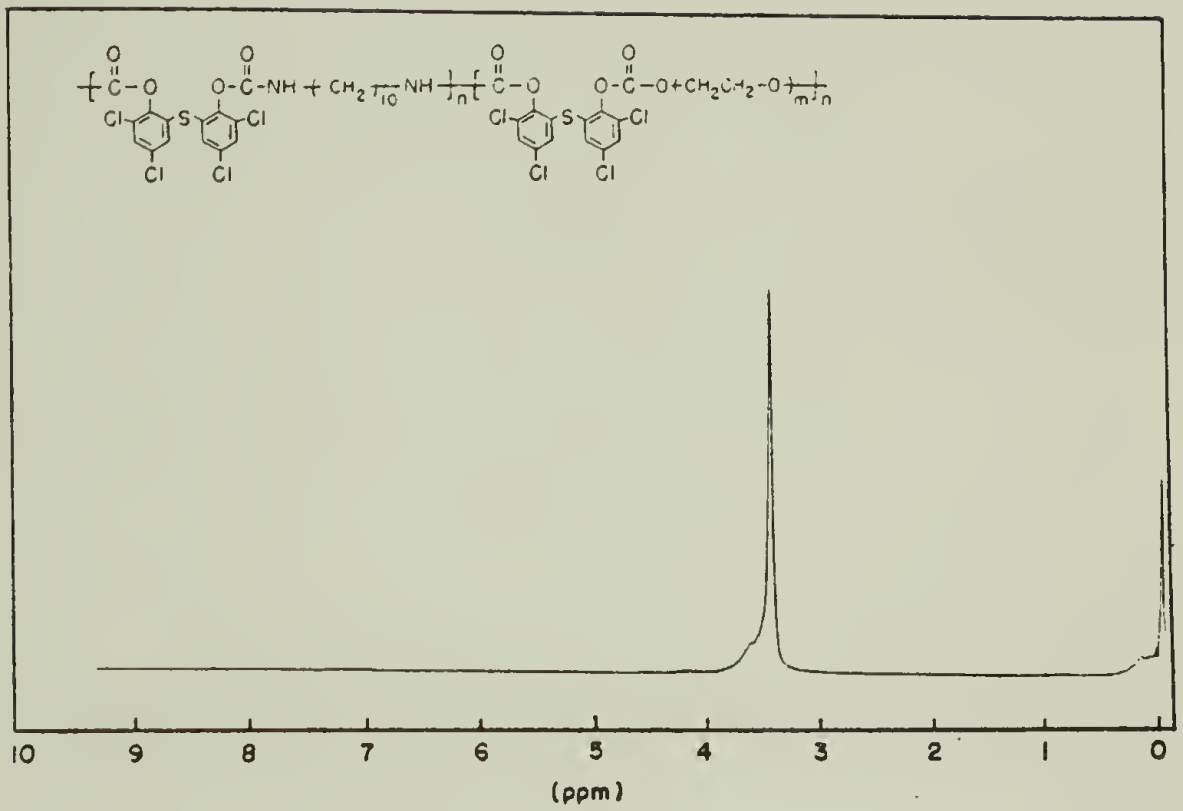
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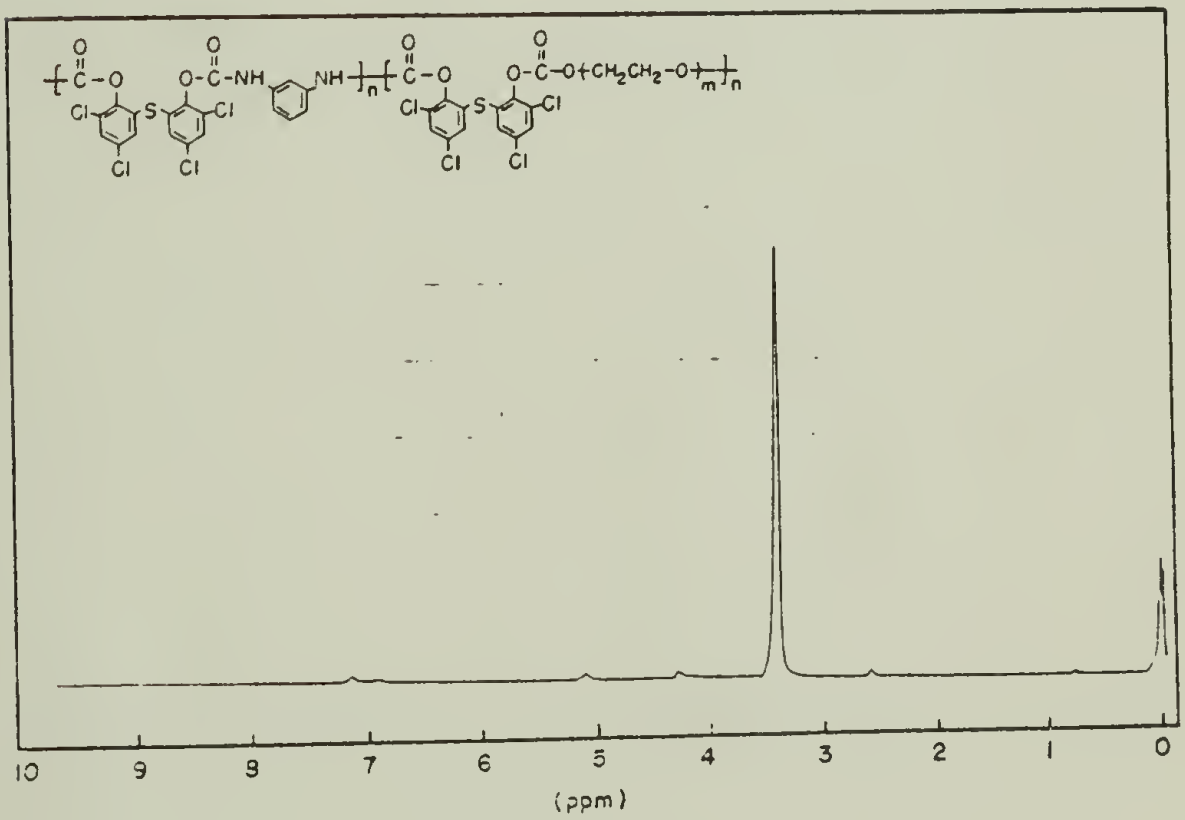
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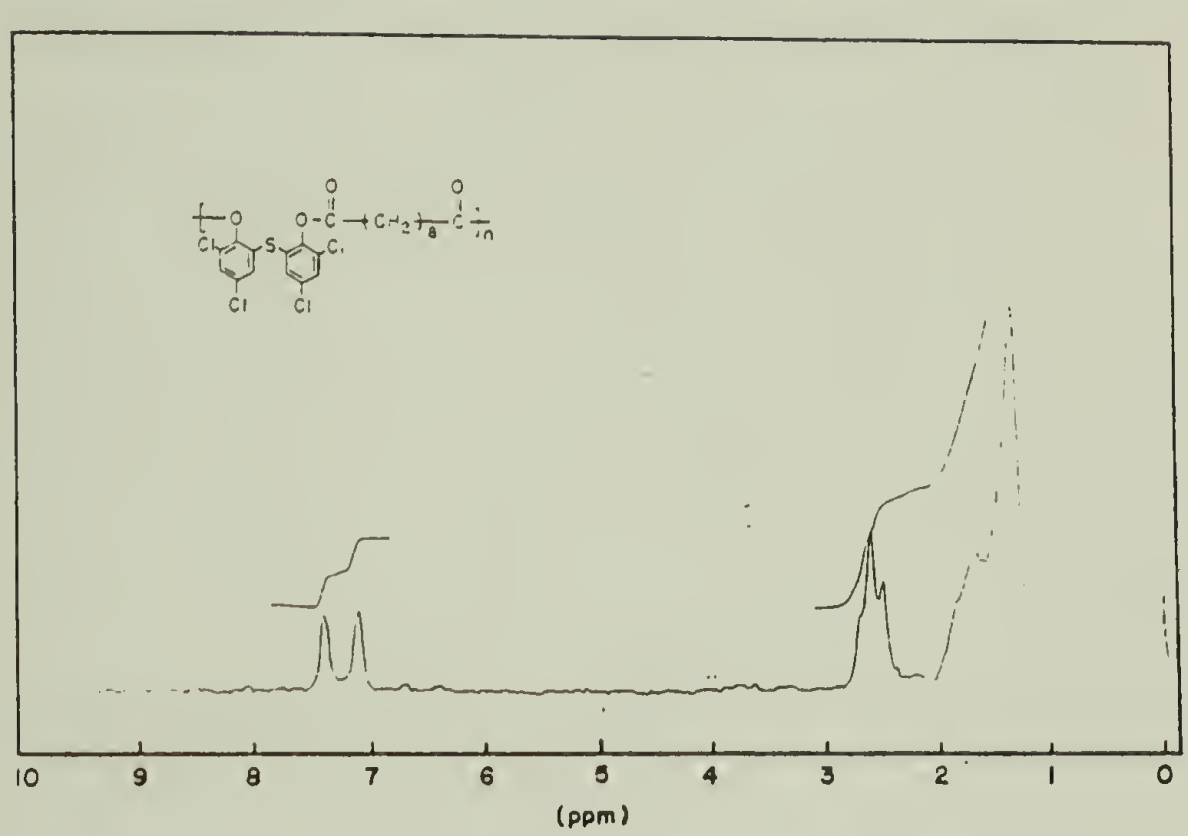
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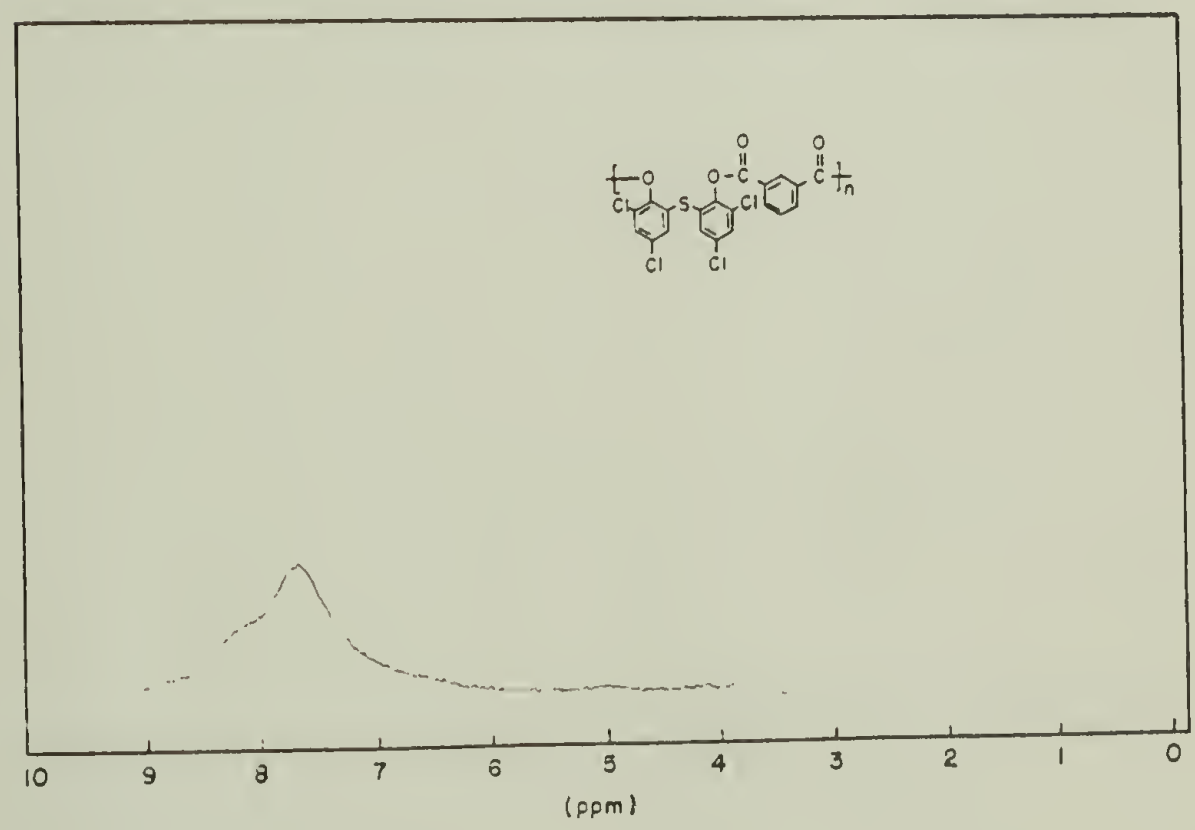
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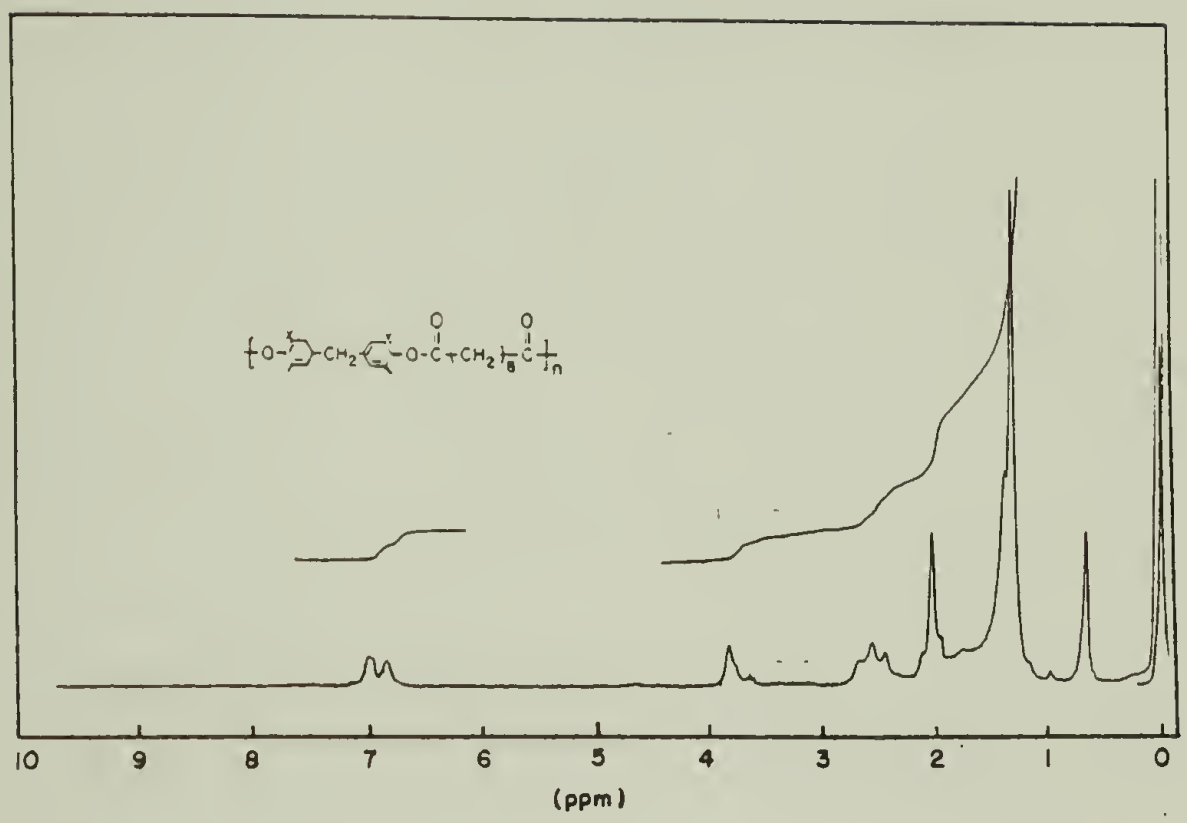
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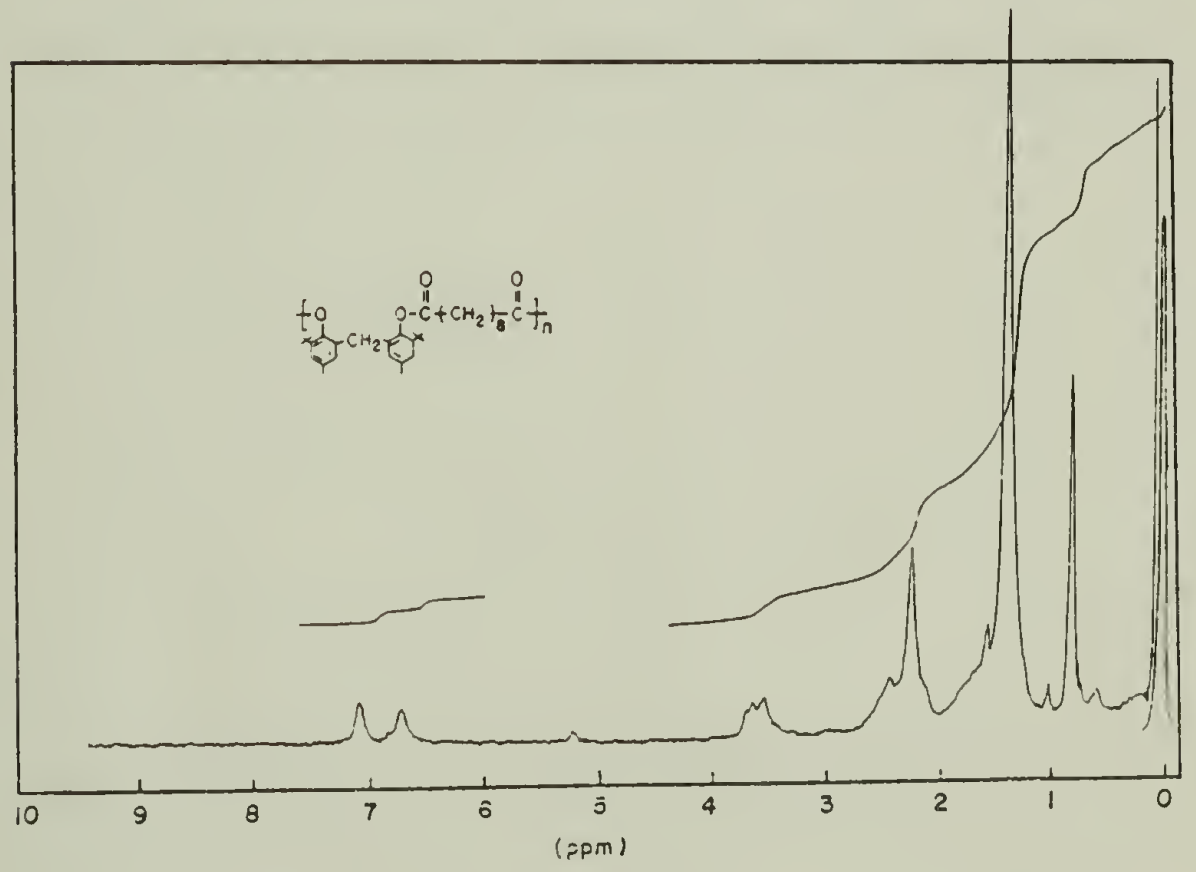
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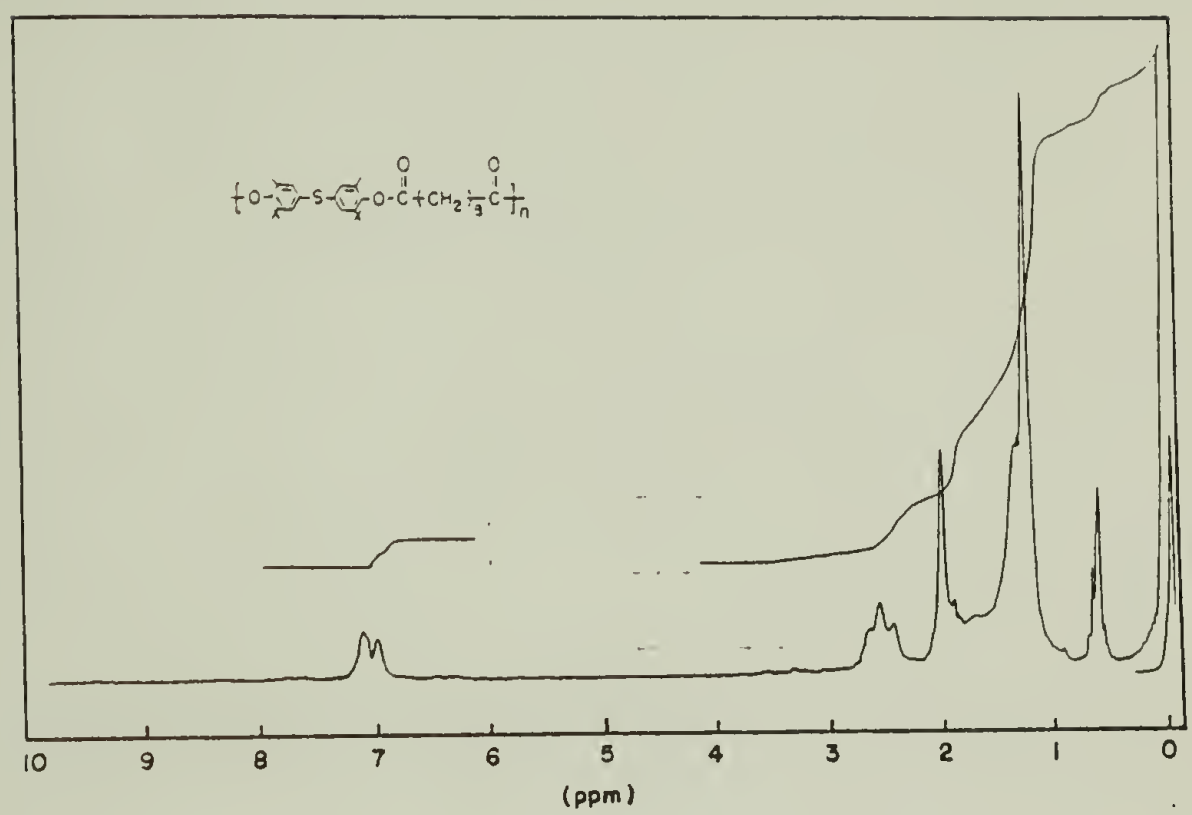
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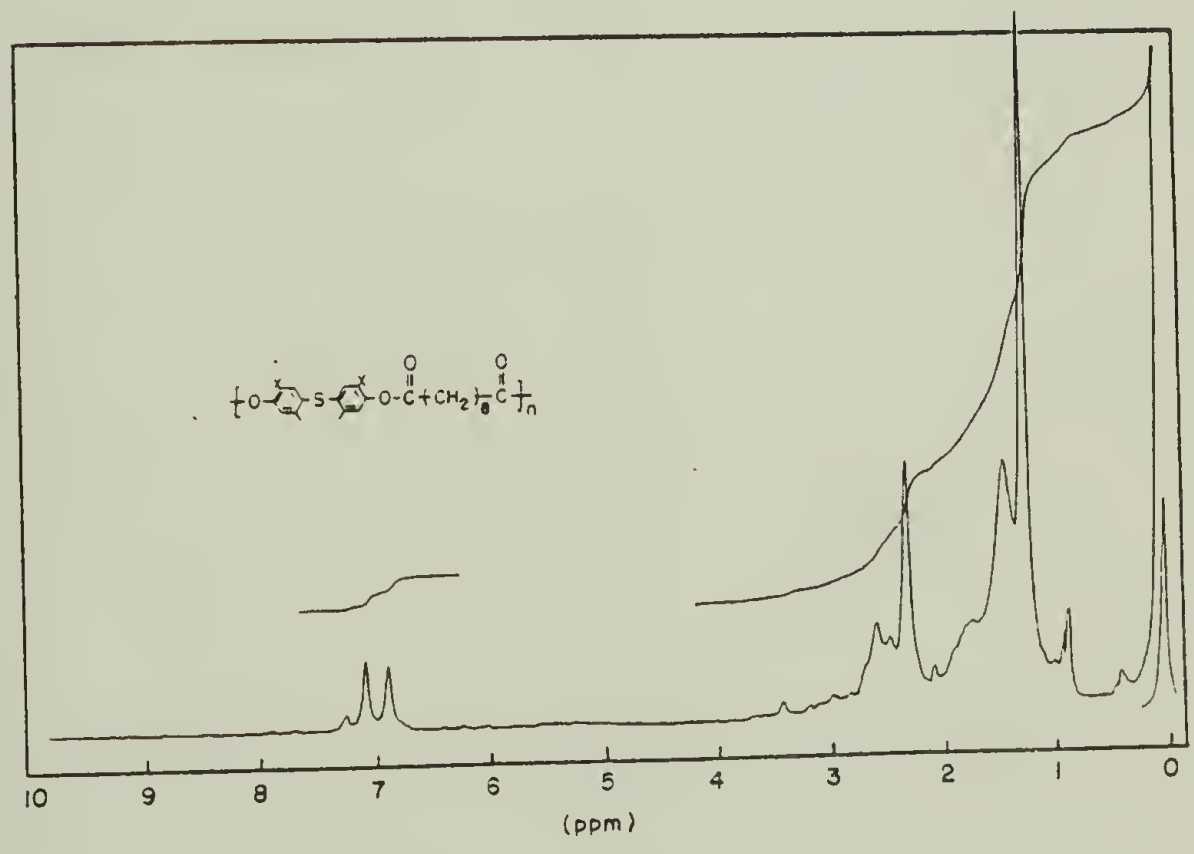
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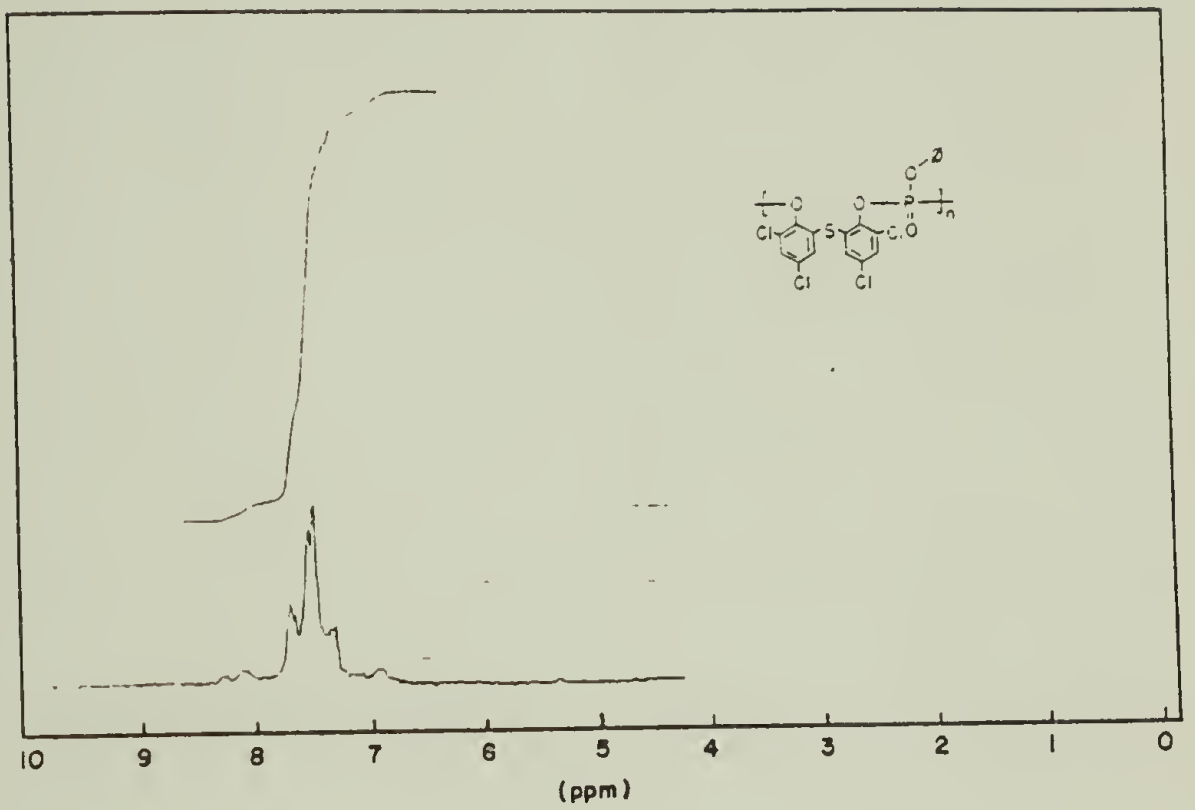
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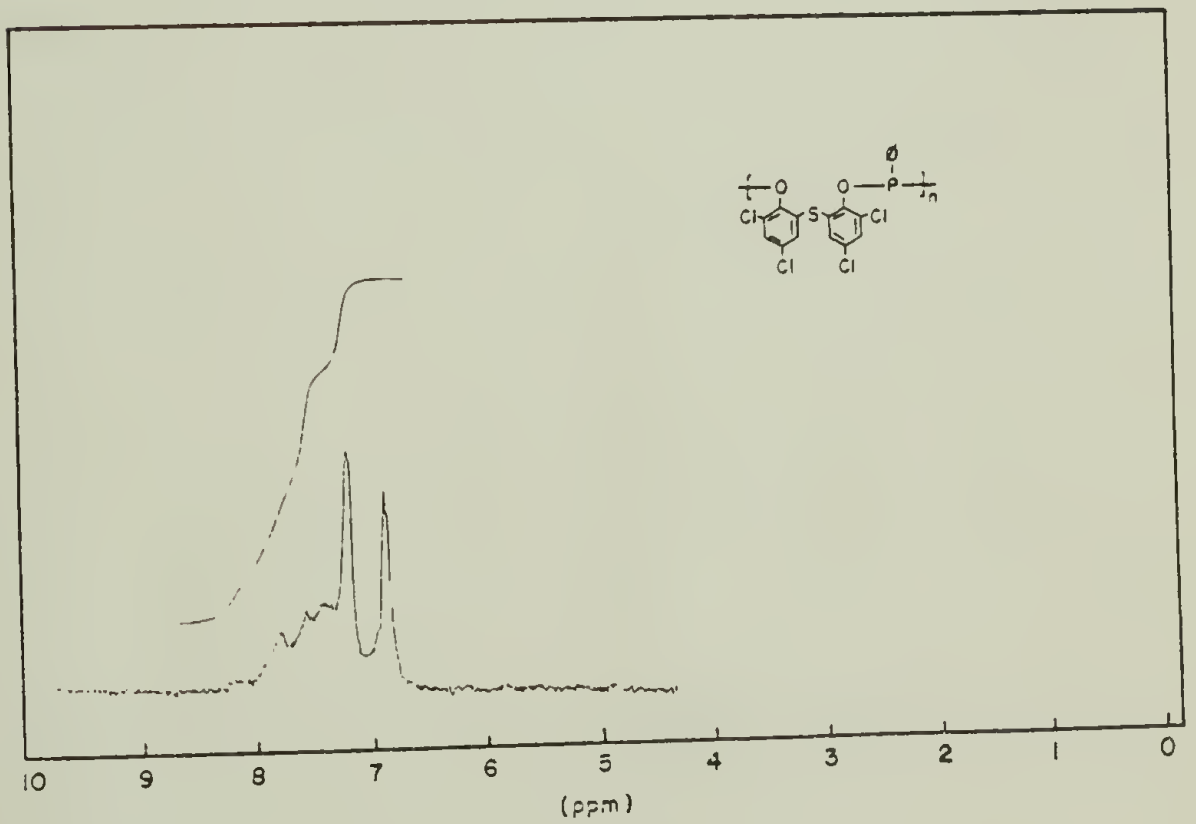
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A P P E N D I X B

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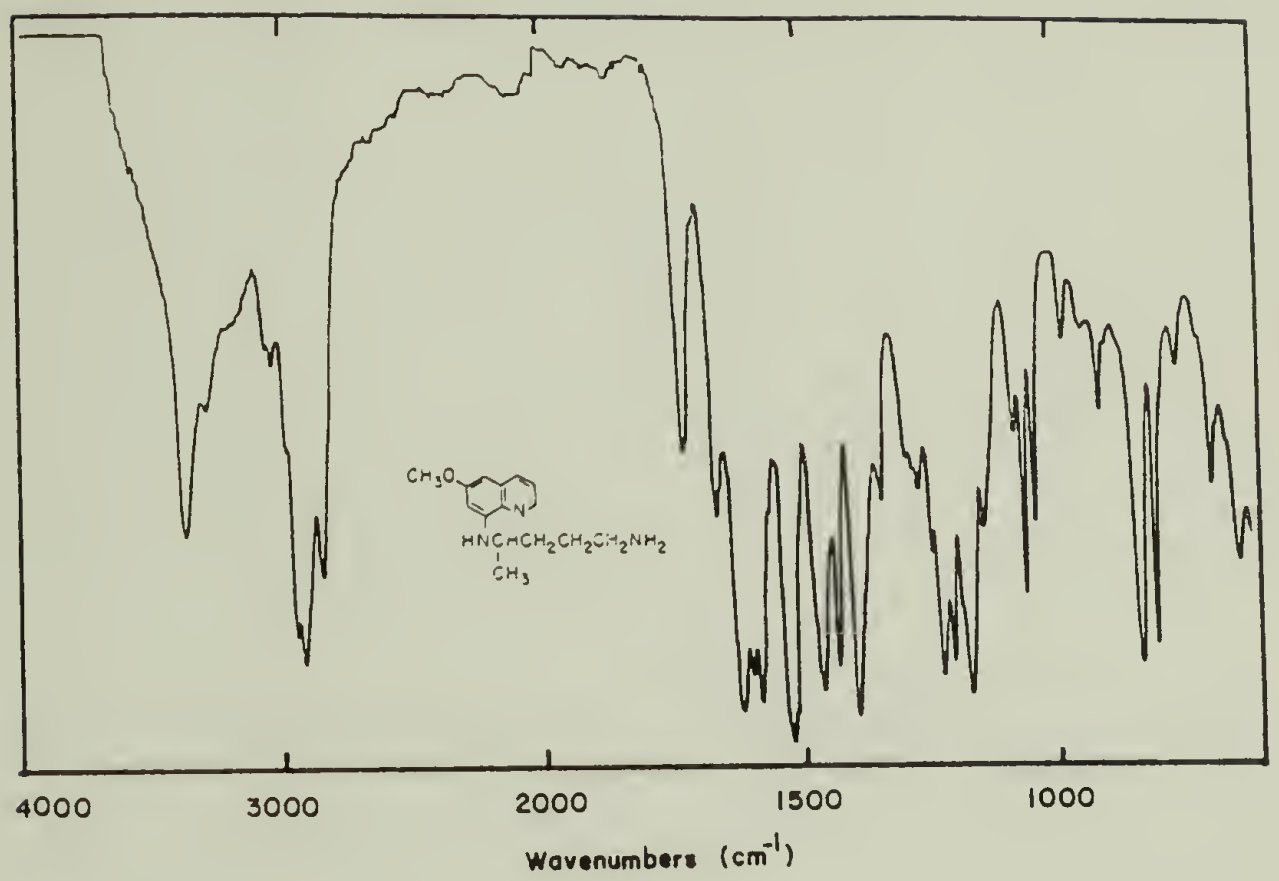
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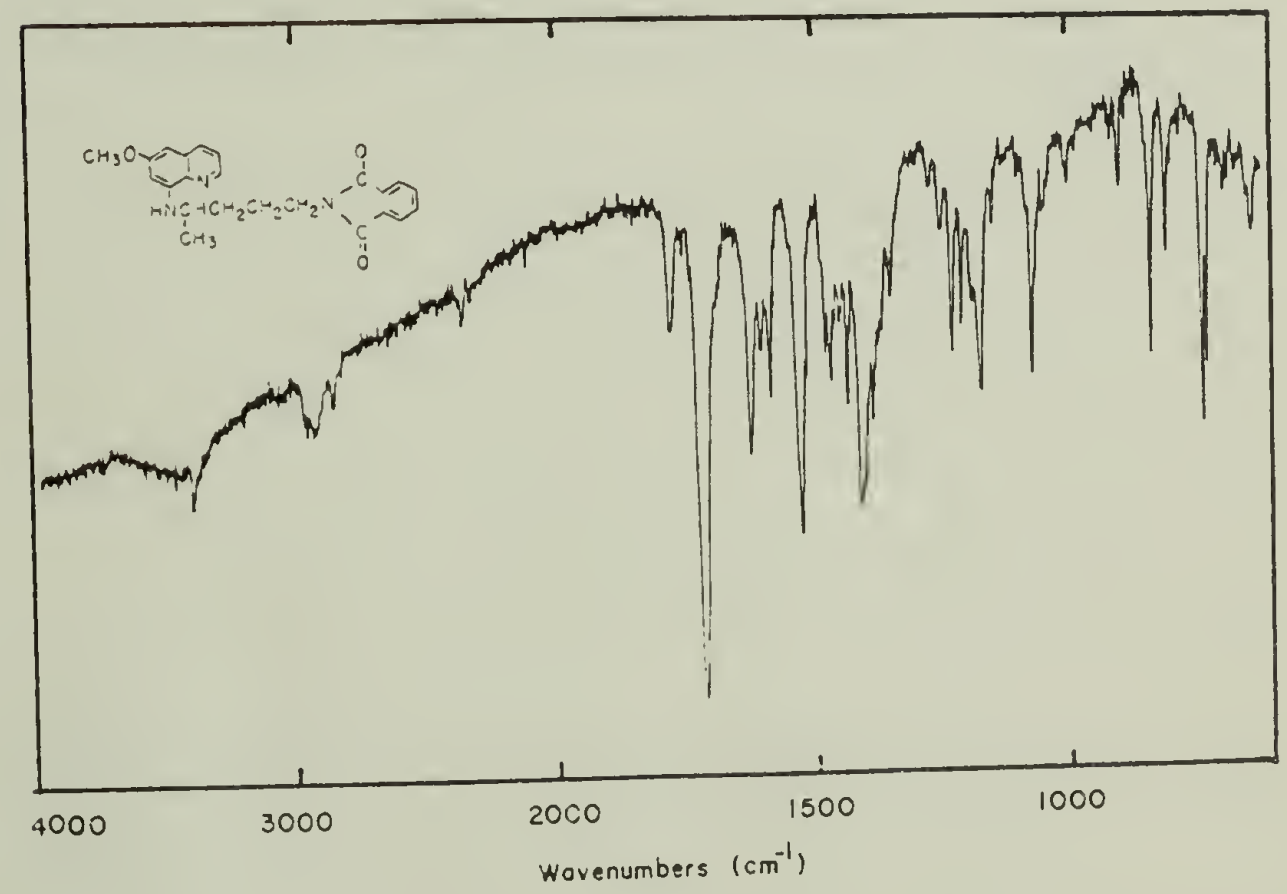
Wavenumbers (cm-1)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CH3
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C
C
O
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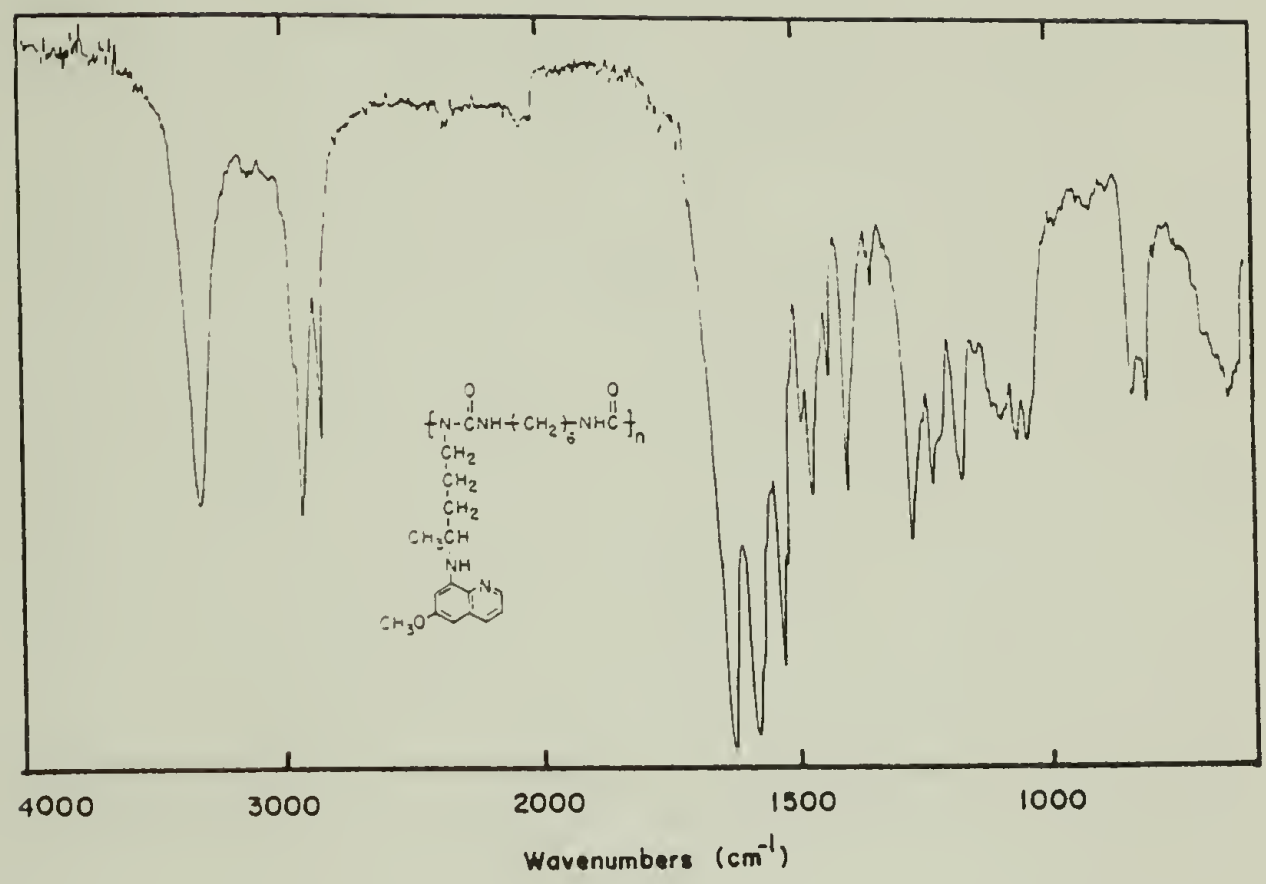
Wavenumbers (cm-1)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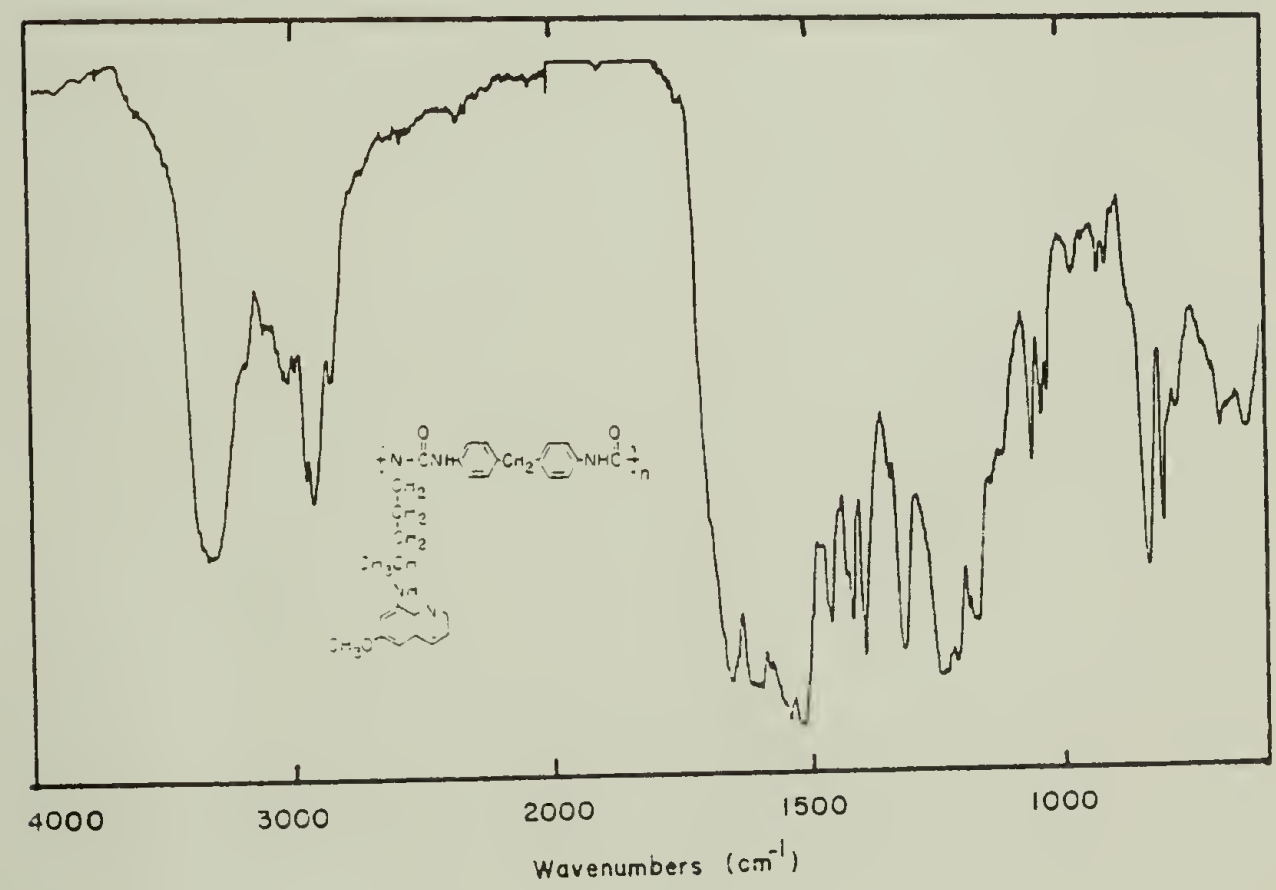
Wavenumbers (cm⁻¹)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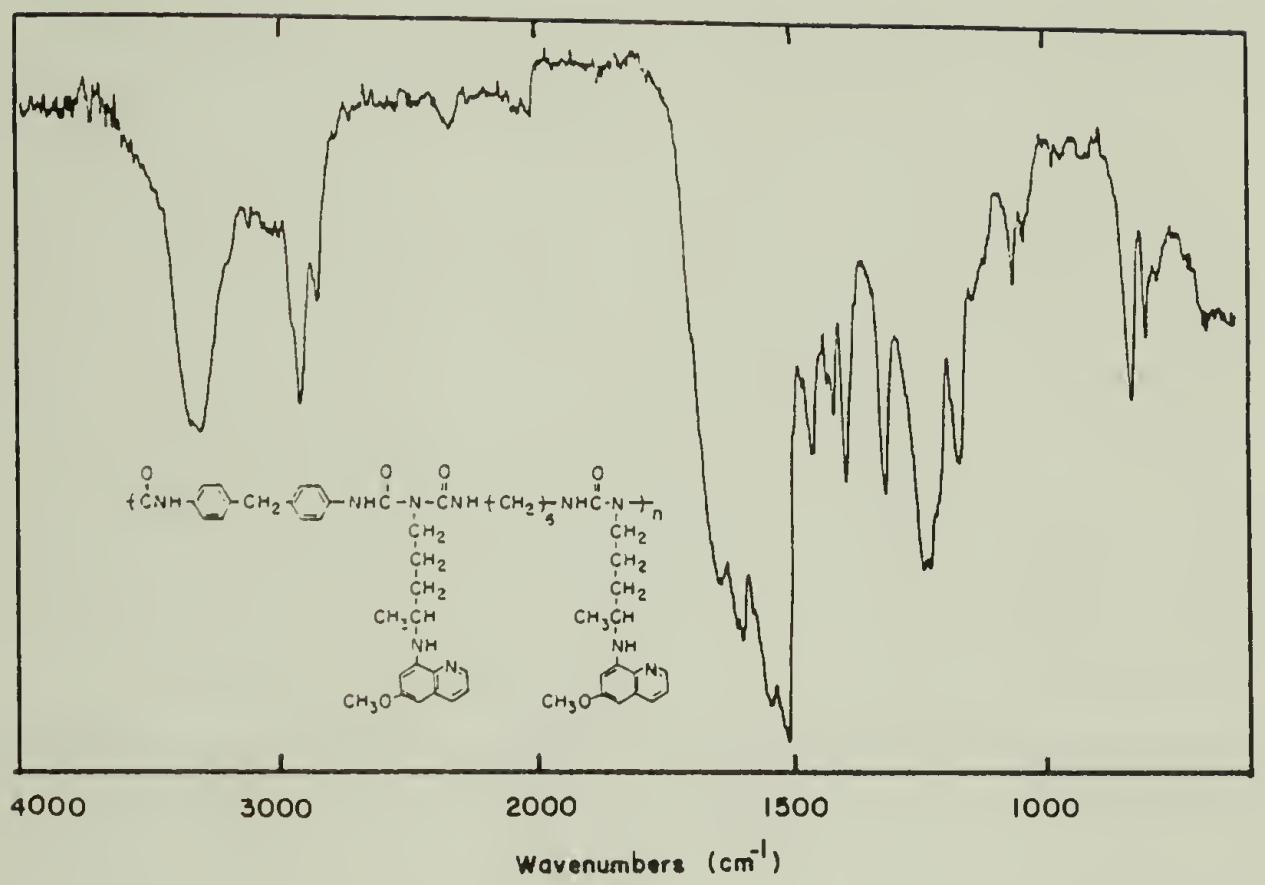
Wavenumbers (cm⁻¹)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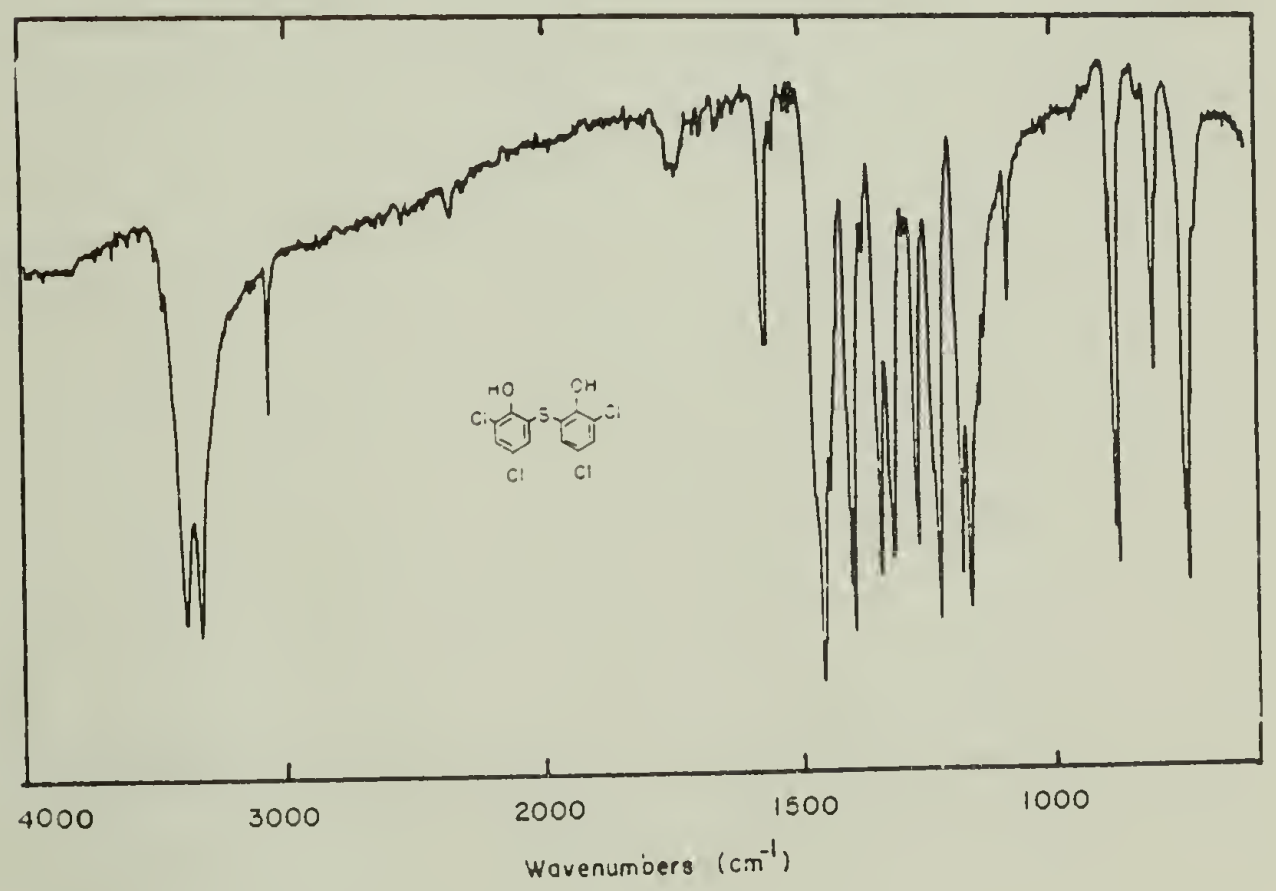
Wavenumbers (cm⁻¹)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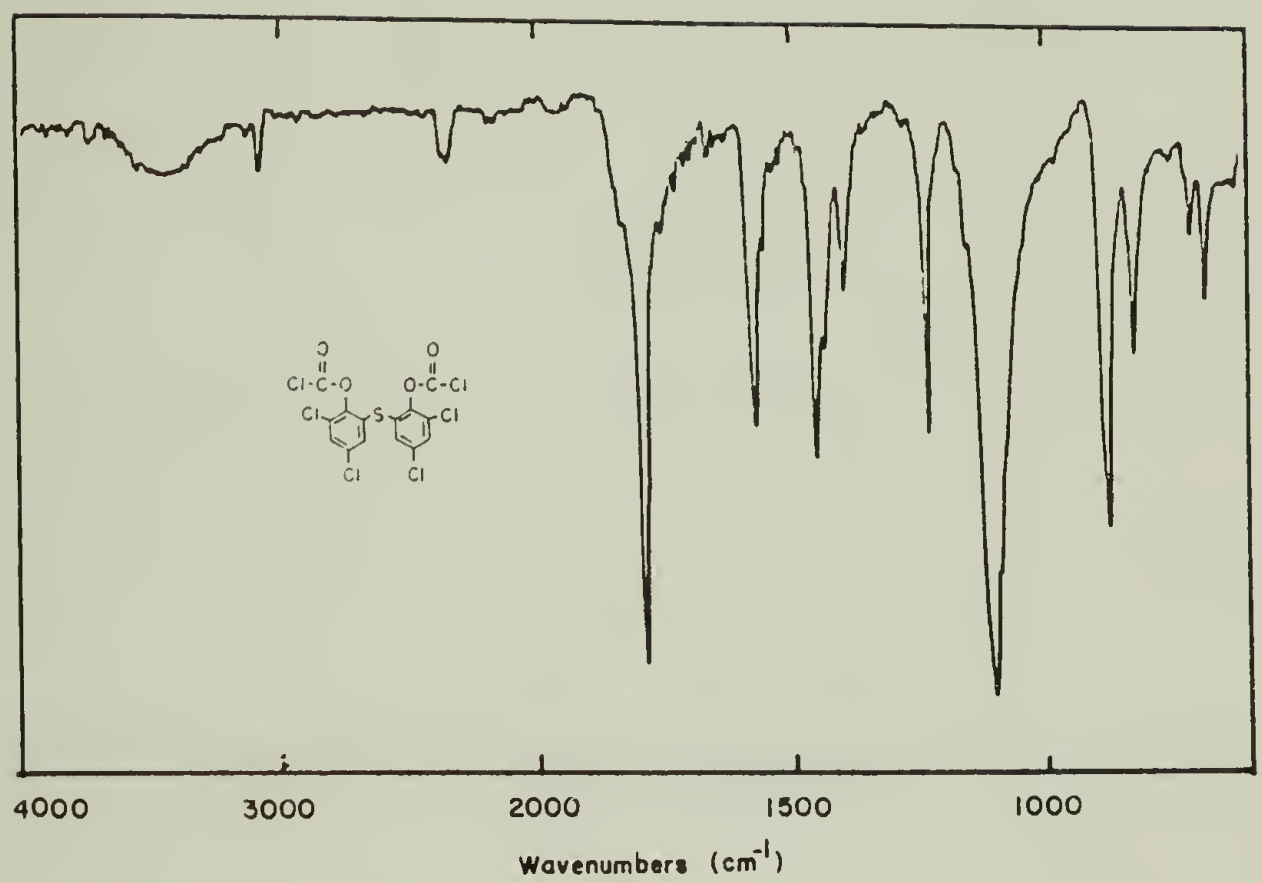
Wavenumbers (cm⁻¹)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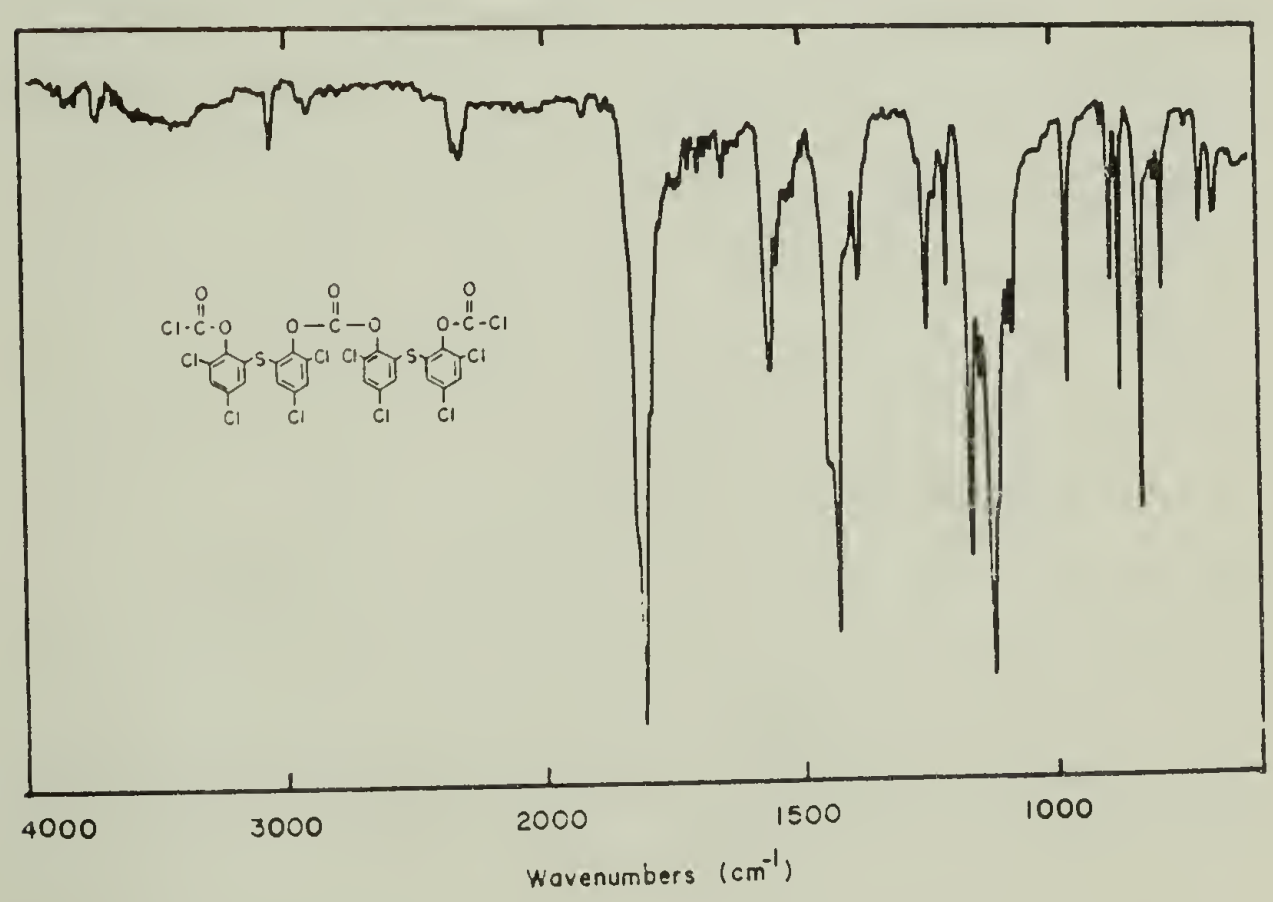
Wavenumbers (cm-1)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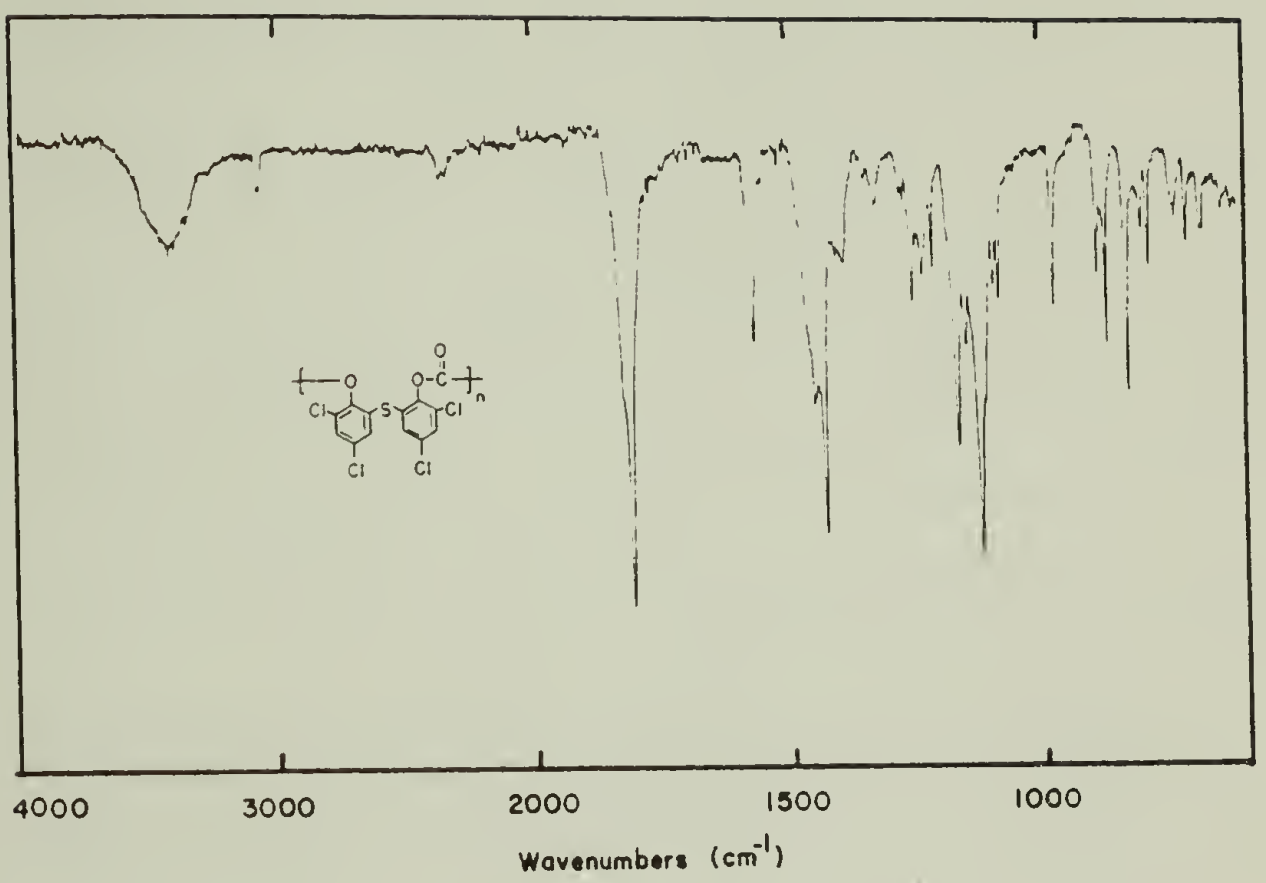
Wavenumbers (cm-1)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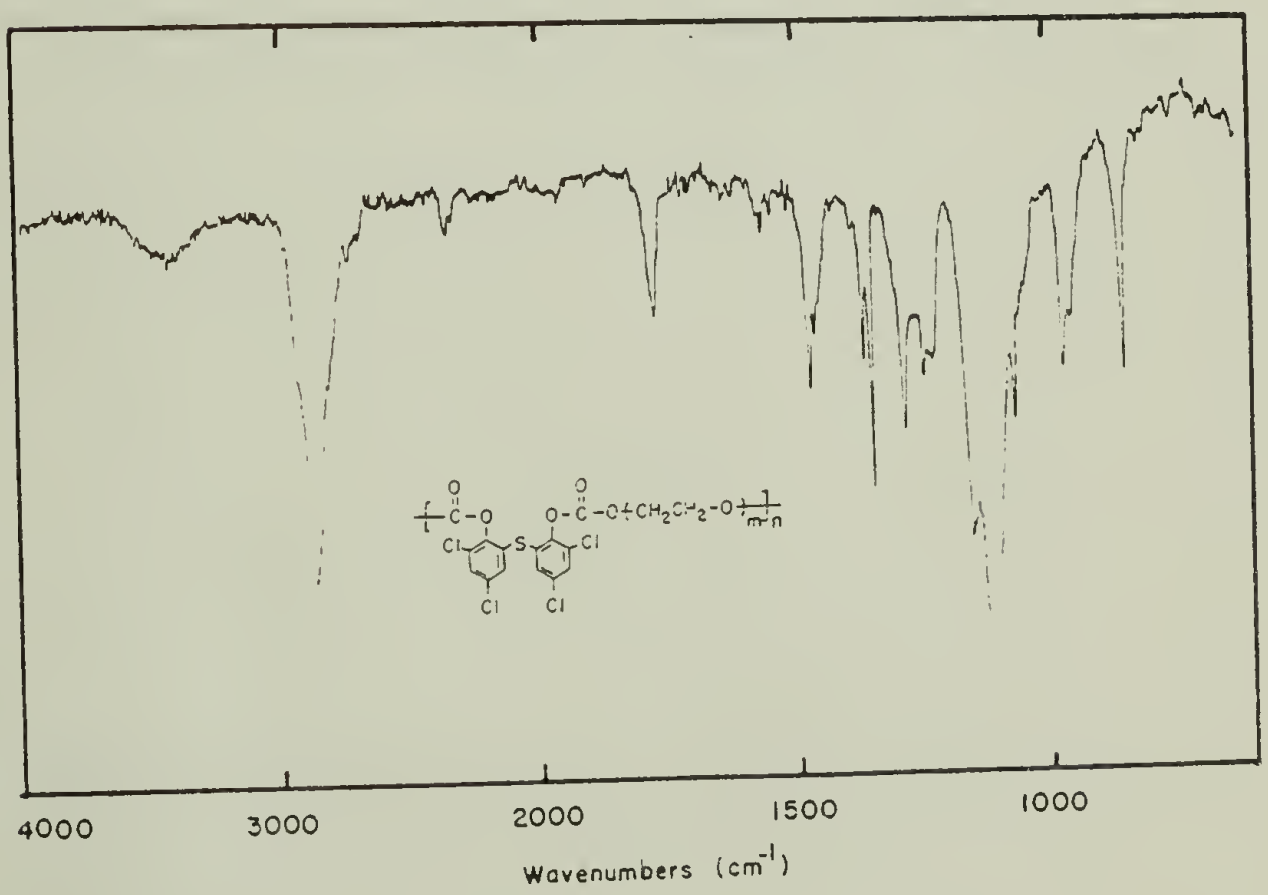
Wavenumbers (cm⁻¹)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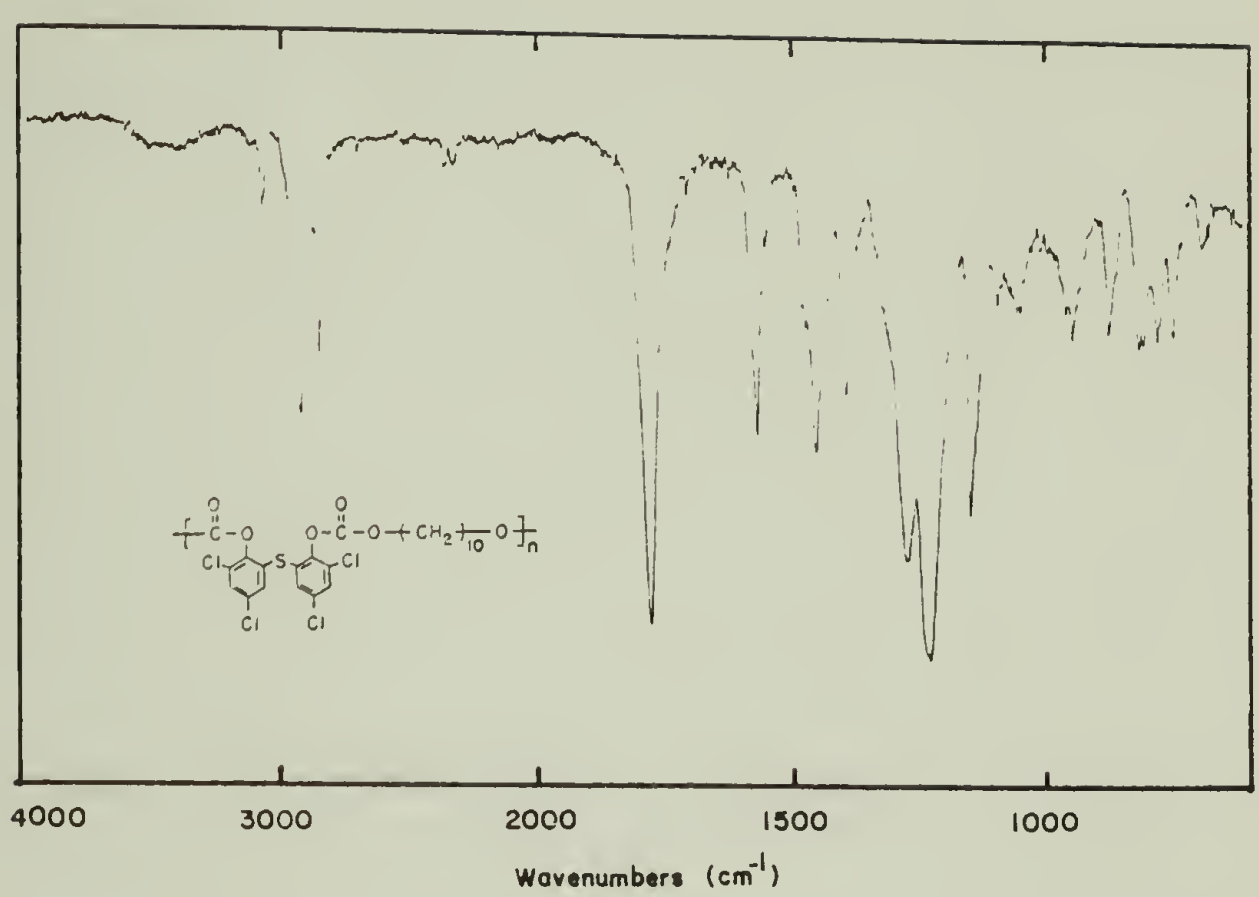
Wavenumbers (cm⁻¹)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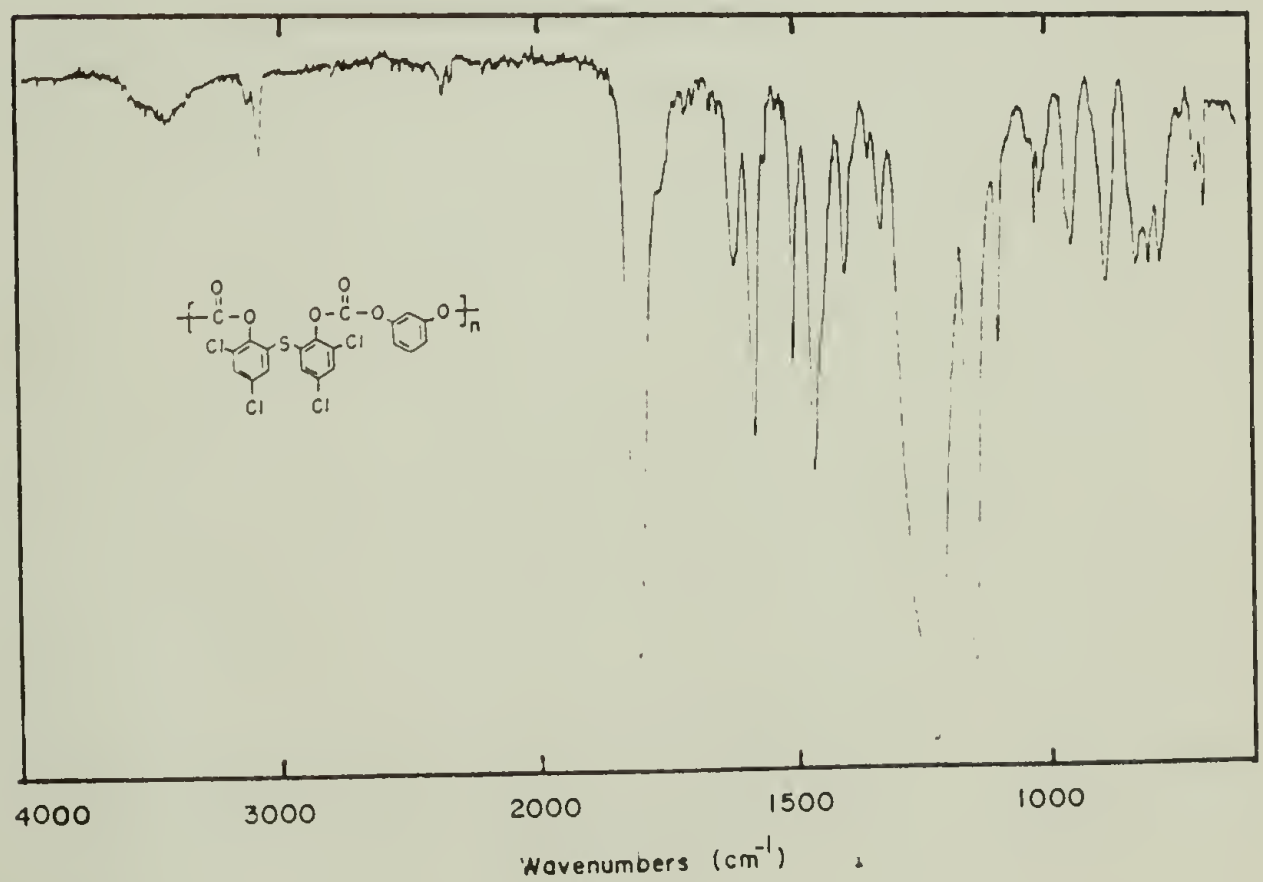
Wavenumbers (cm⁻¹)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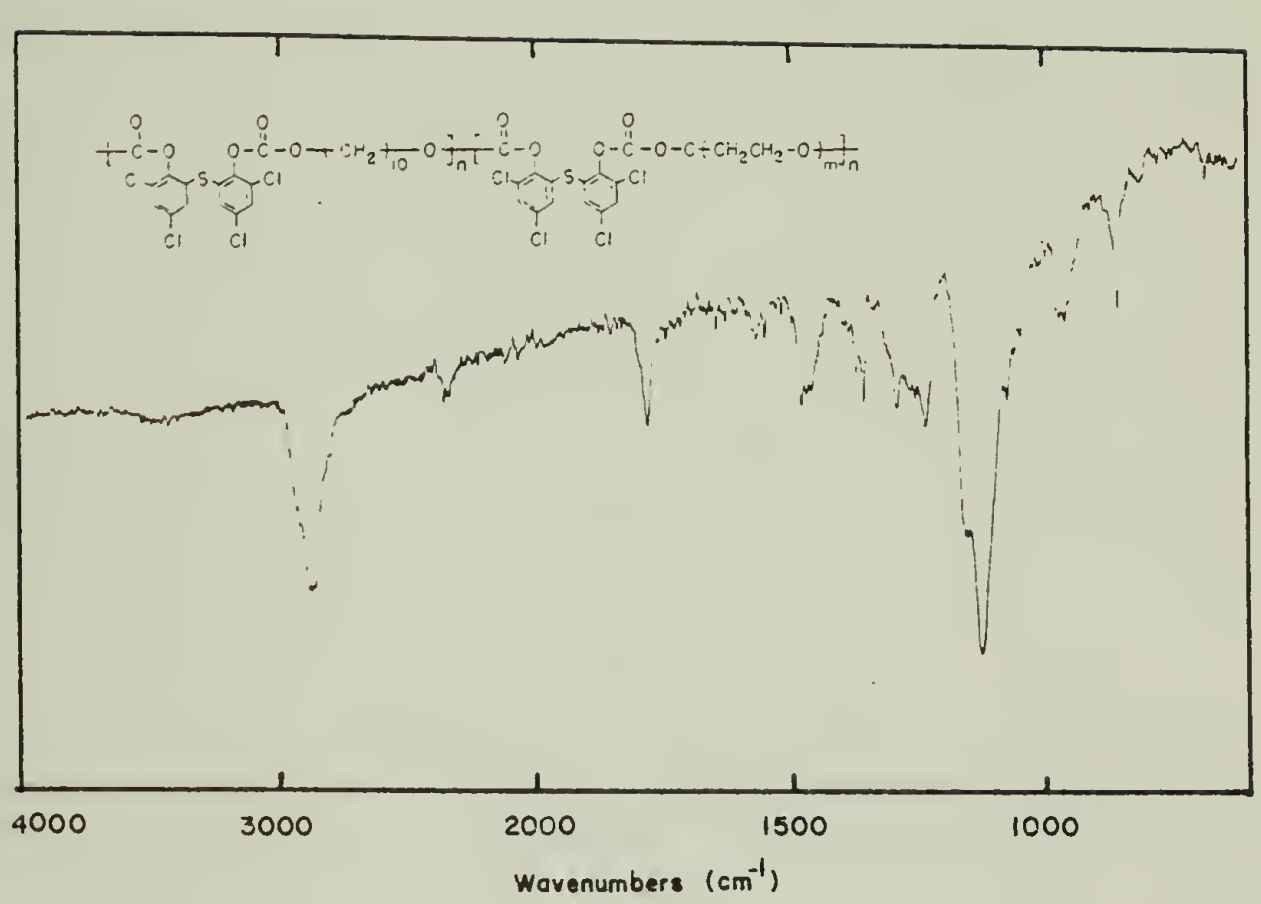
Wavenumbers (cm⁻¹)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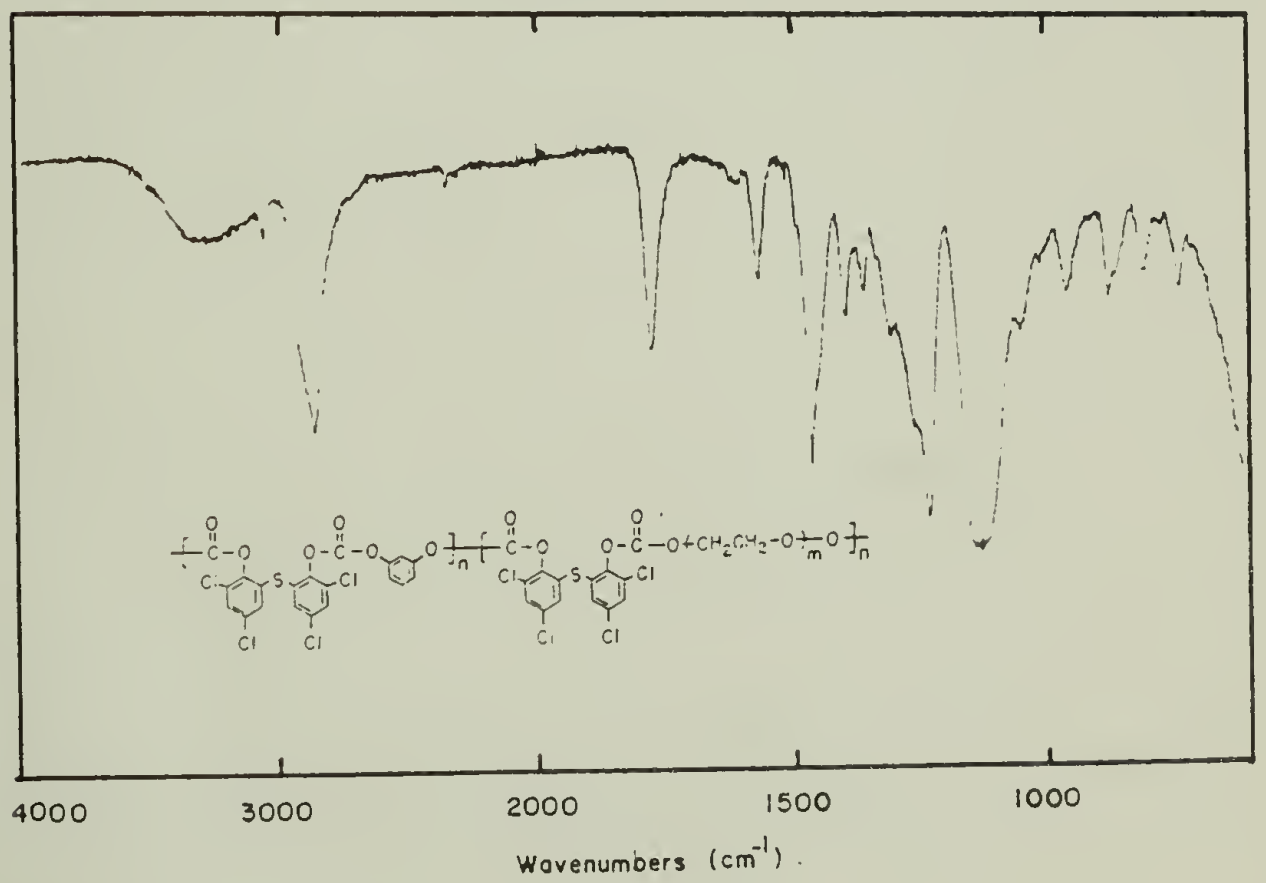
Wavenumbers (cm⁻¹)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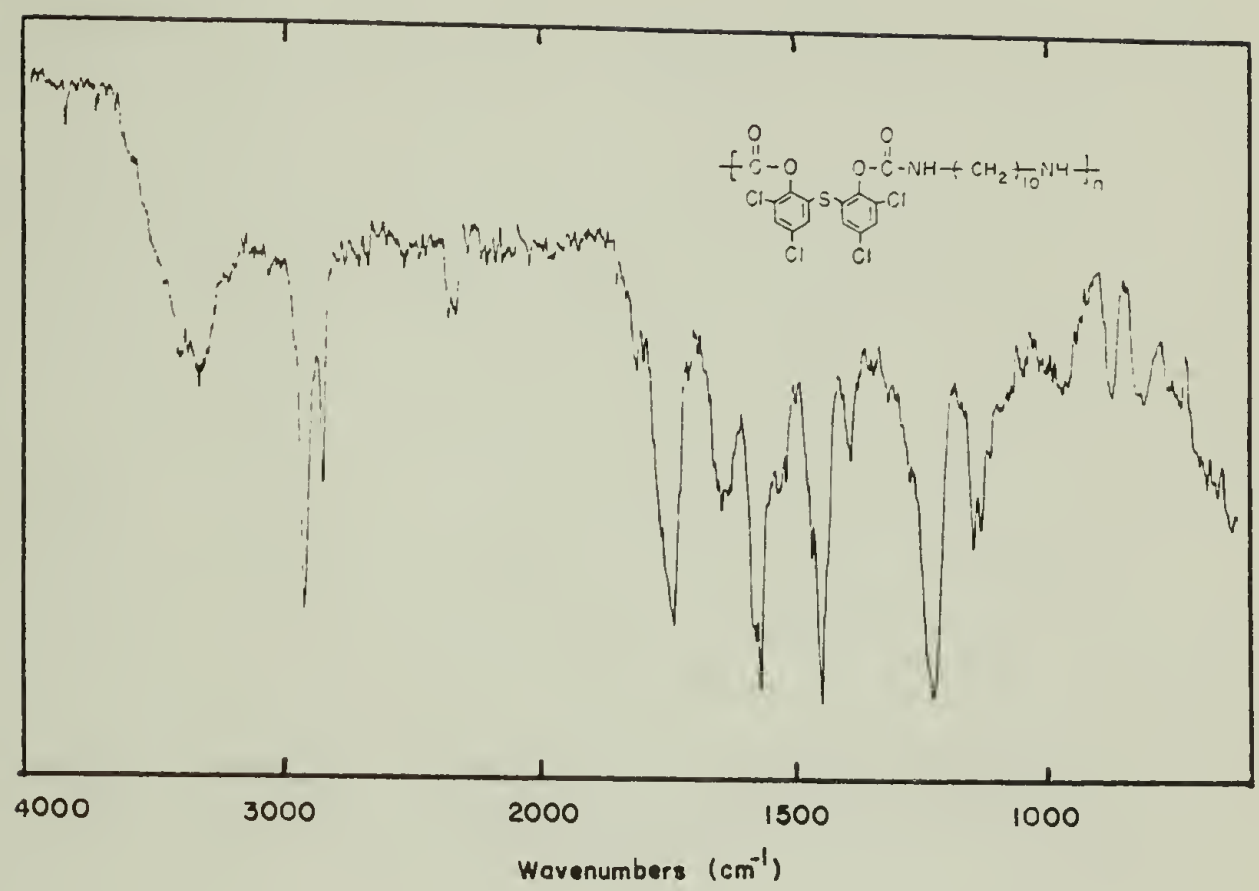
Wavenumbers (cm⁻¹)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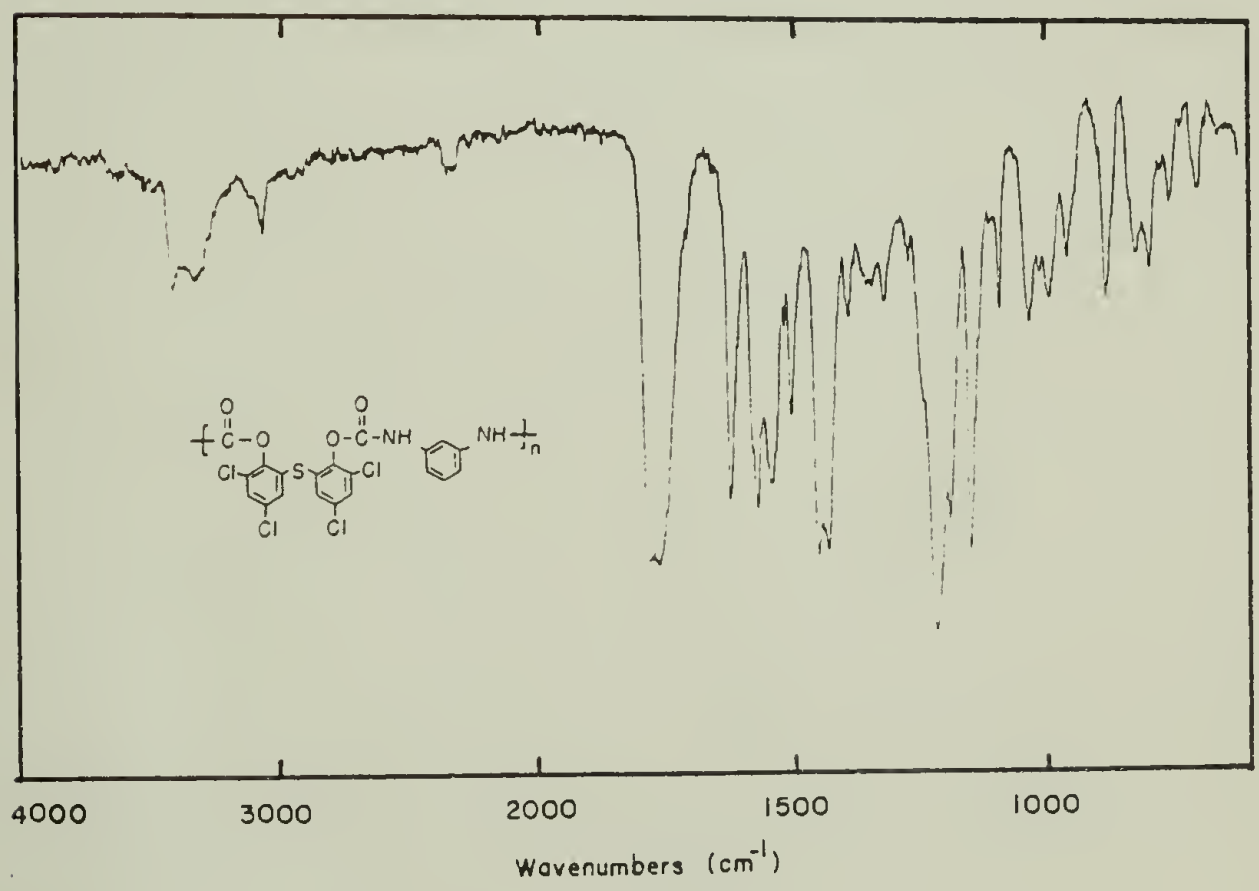
Wavenumbers (cm⁻¹)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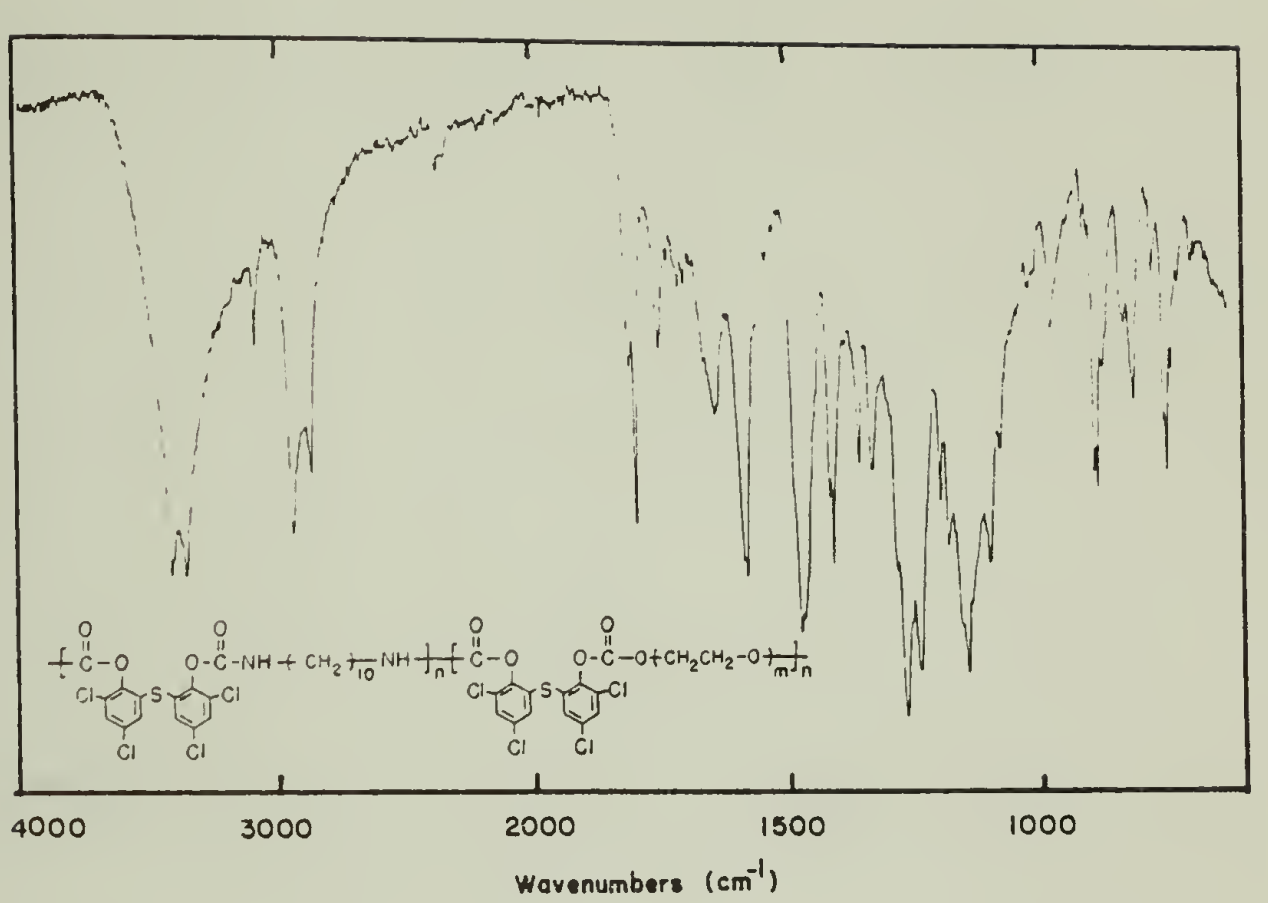
Wavenumbers (cm⁻¹)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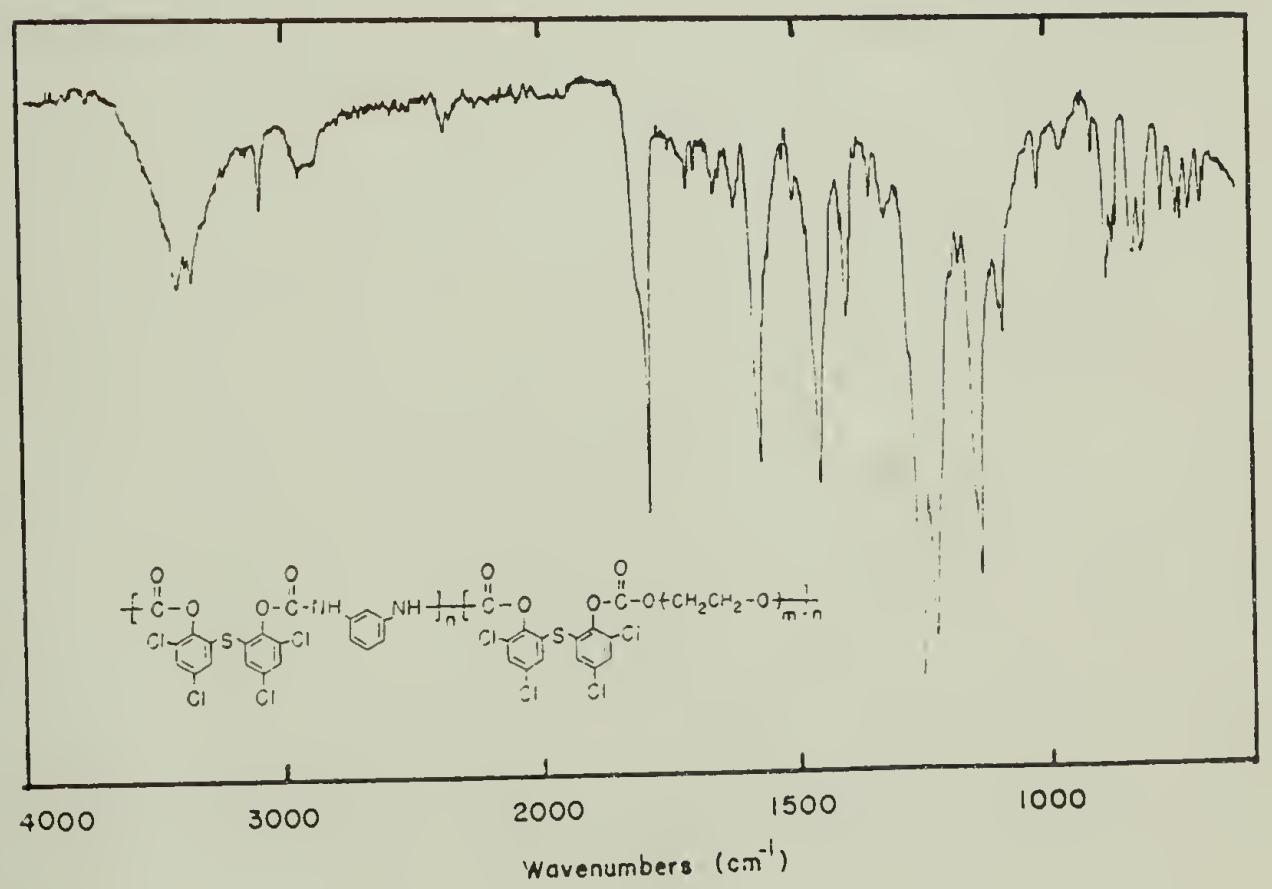
Wavenumbers (cm⁻¹)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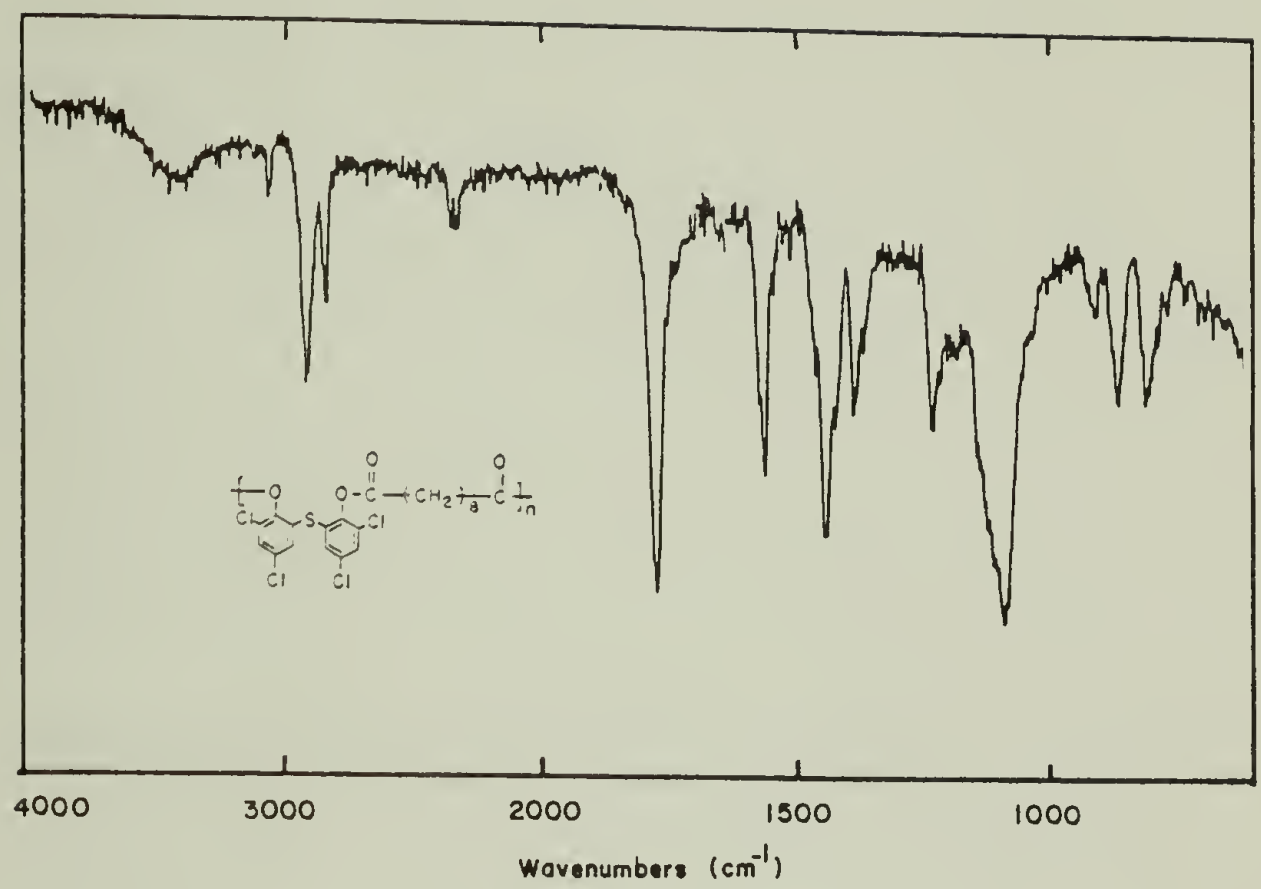
Wavenumbers (cm⁻¹)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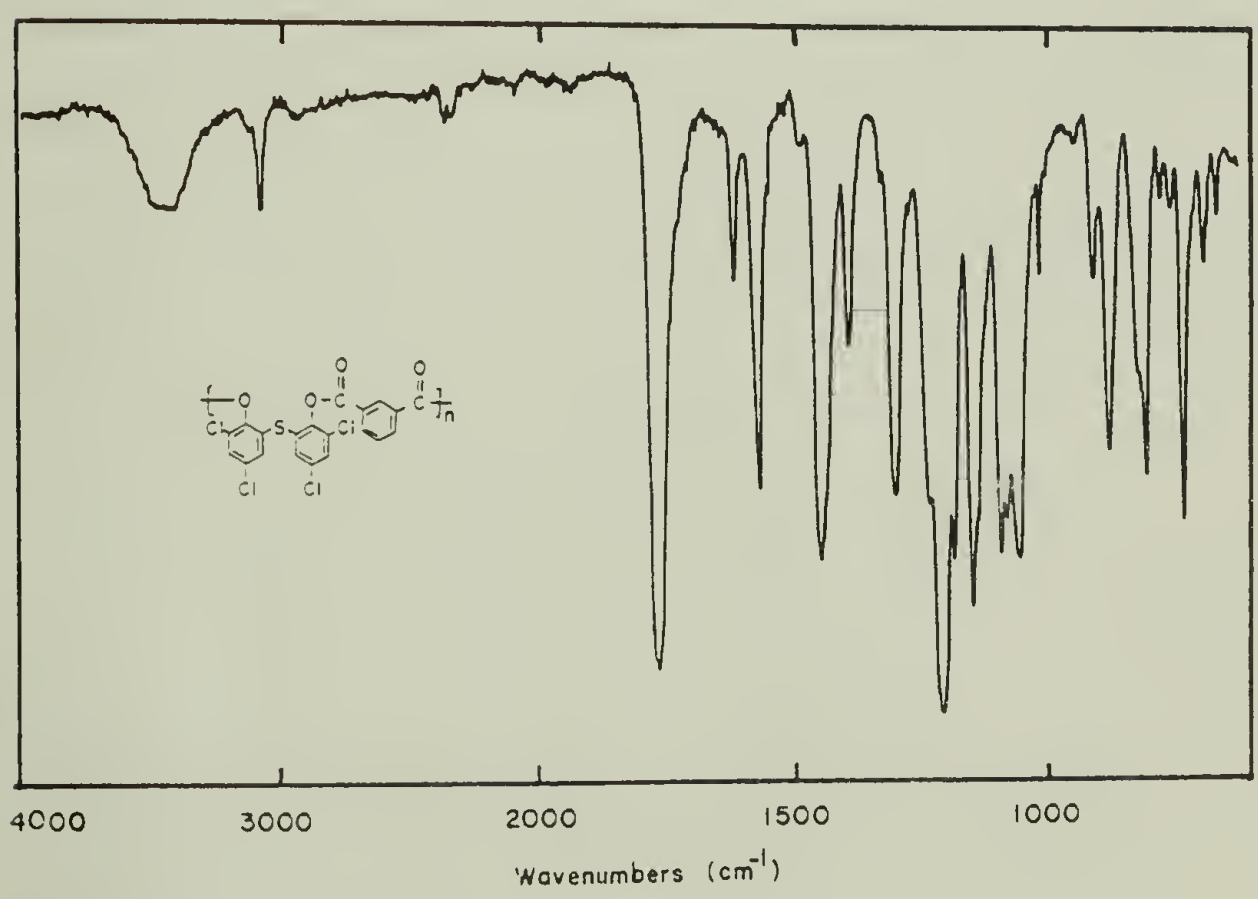
Wavenumbers (cm⁻¹)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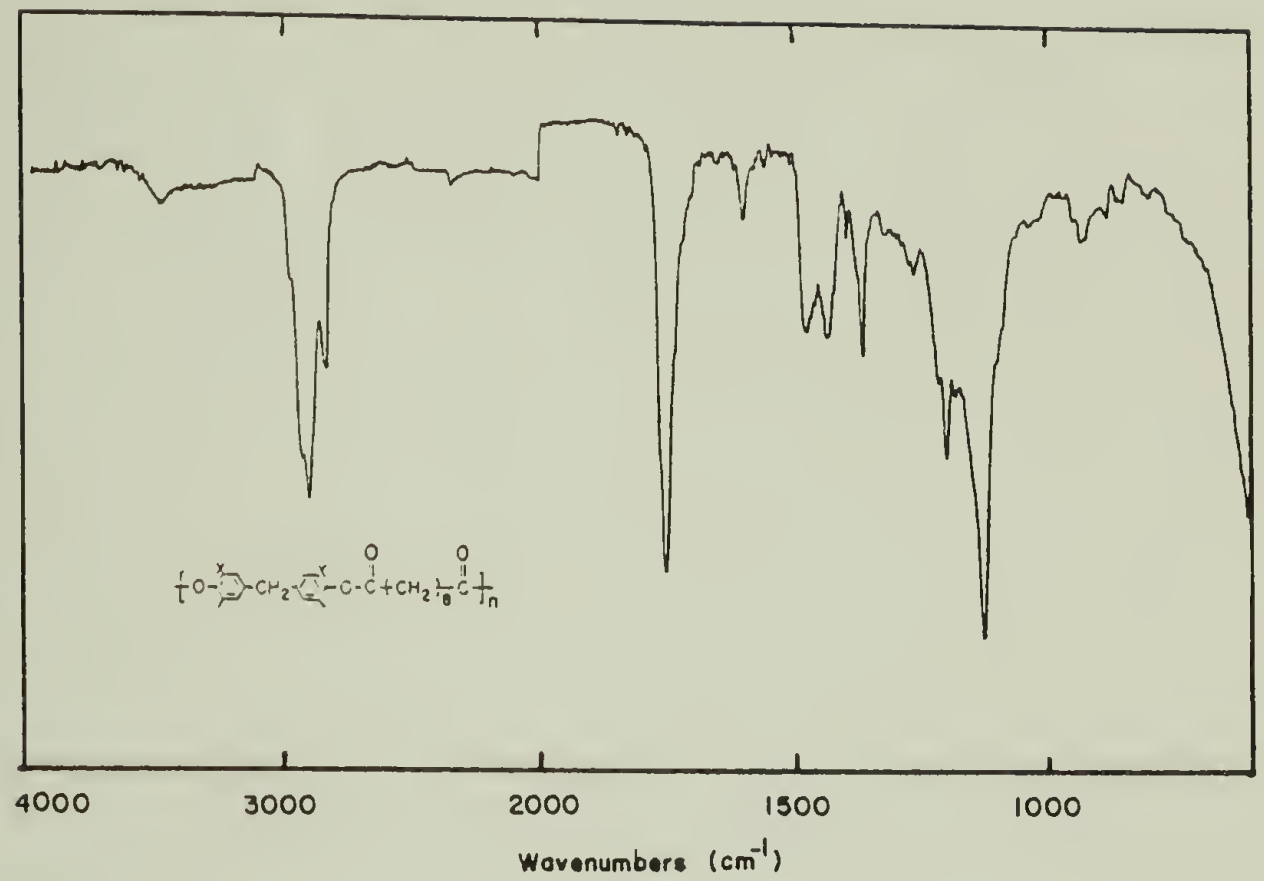
Wavenumbers (cm⁻¹)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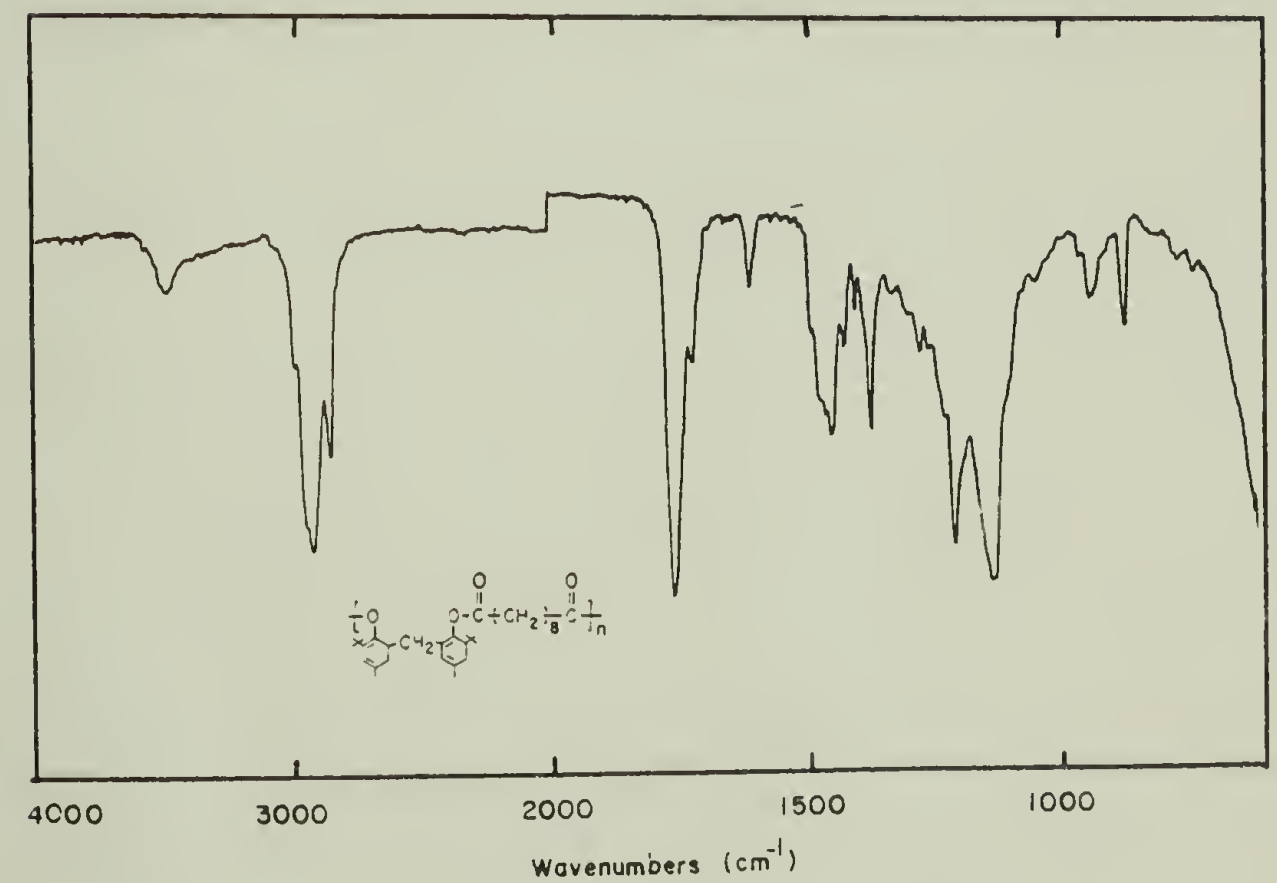
Wavenumbers (cm⁻¹)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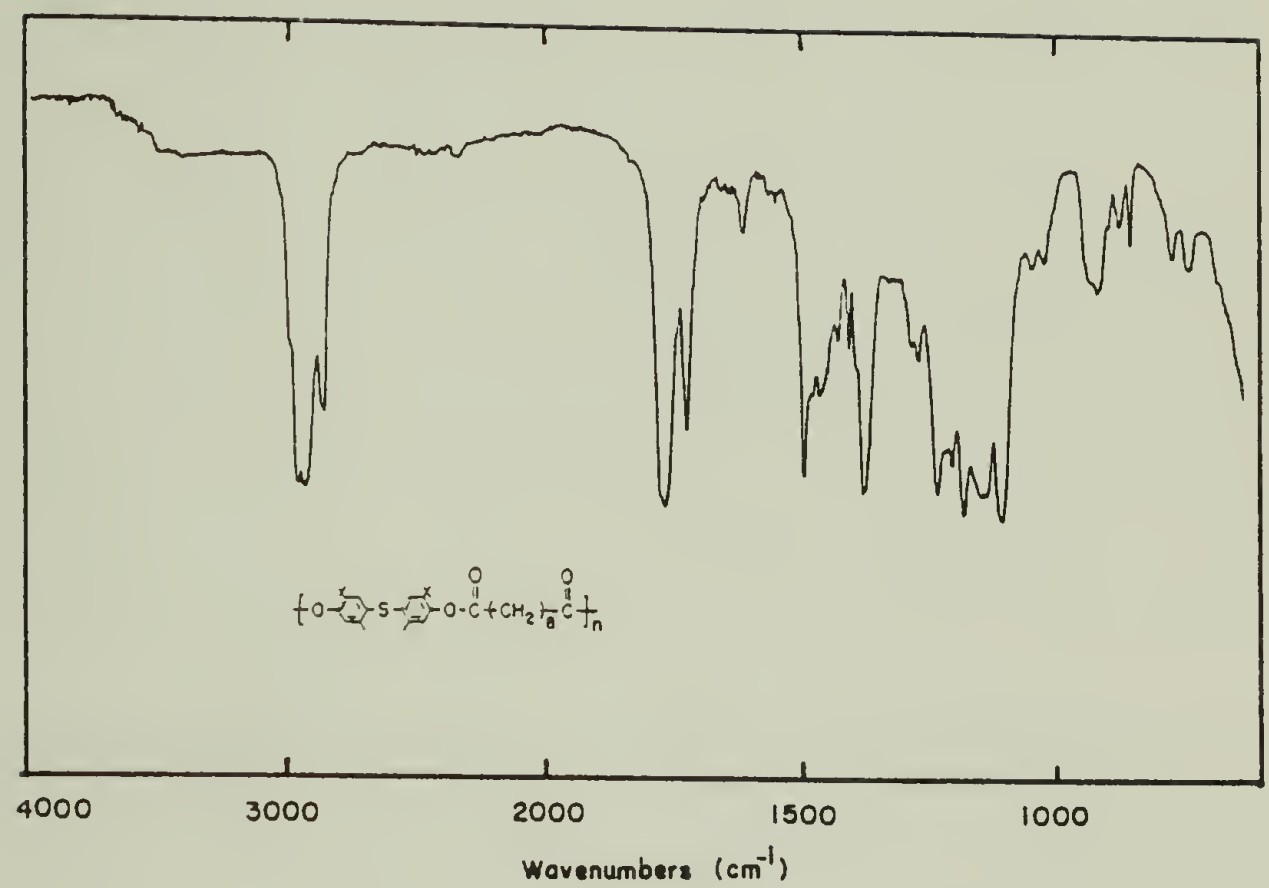
Wavenumbers (cm⁻¹)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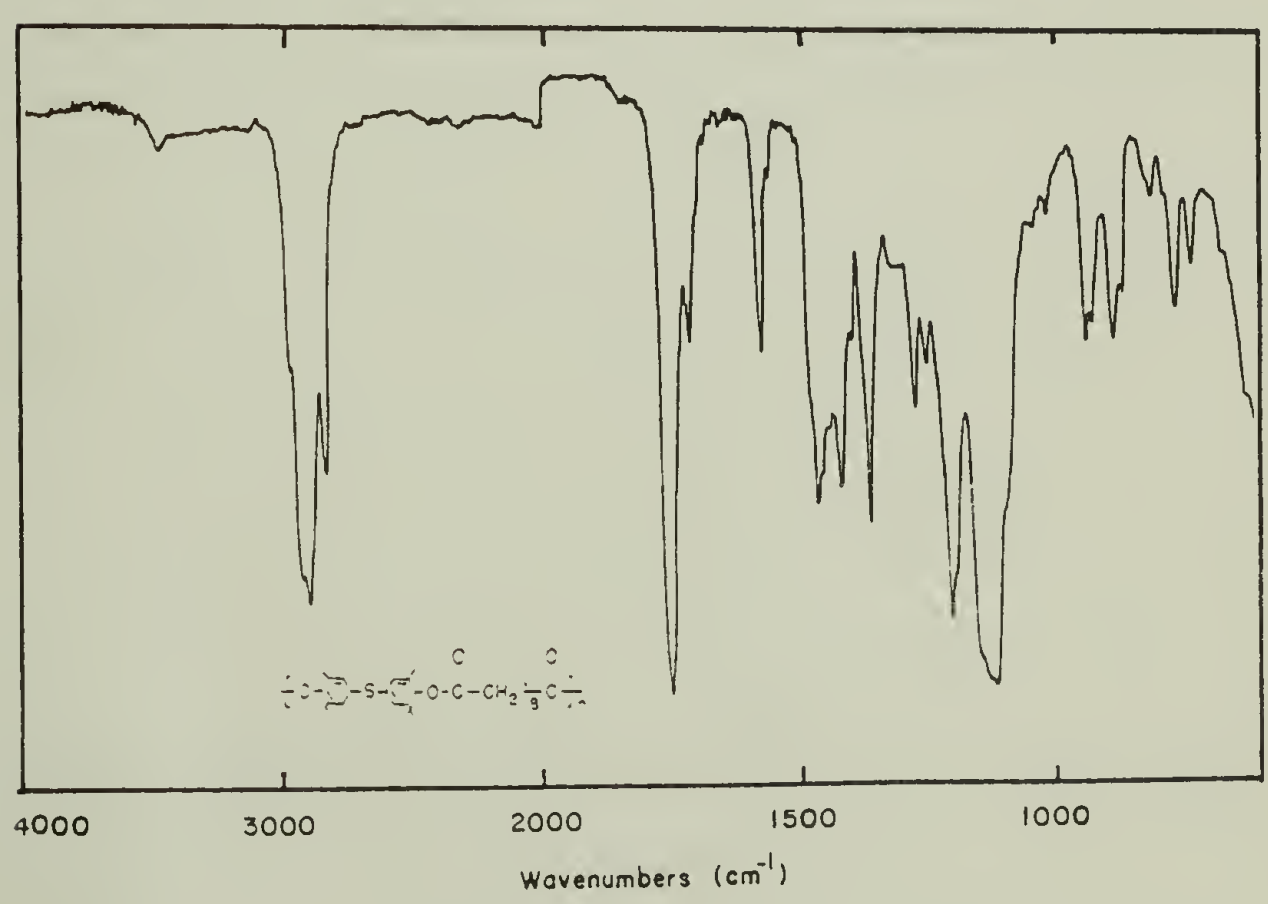
Wavenumbers (cm⁻¹)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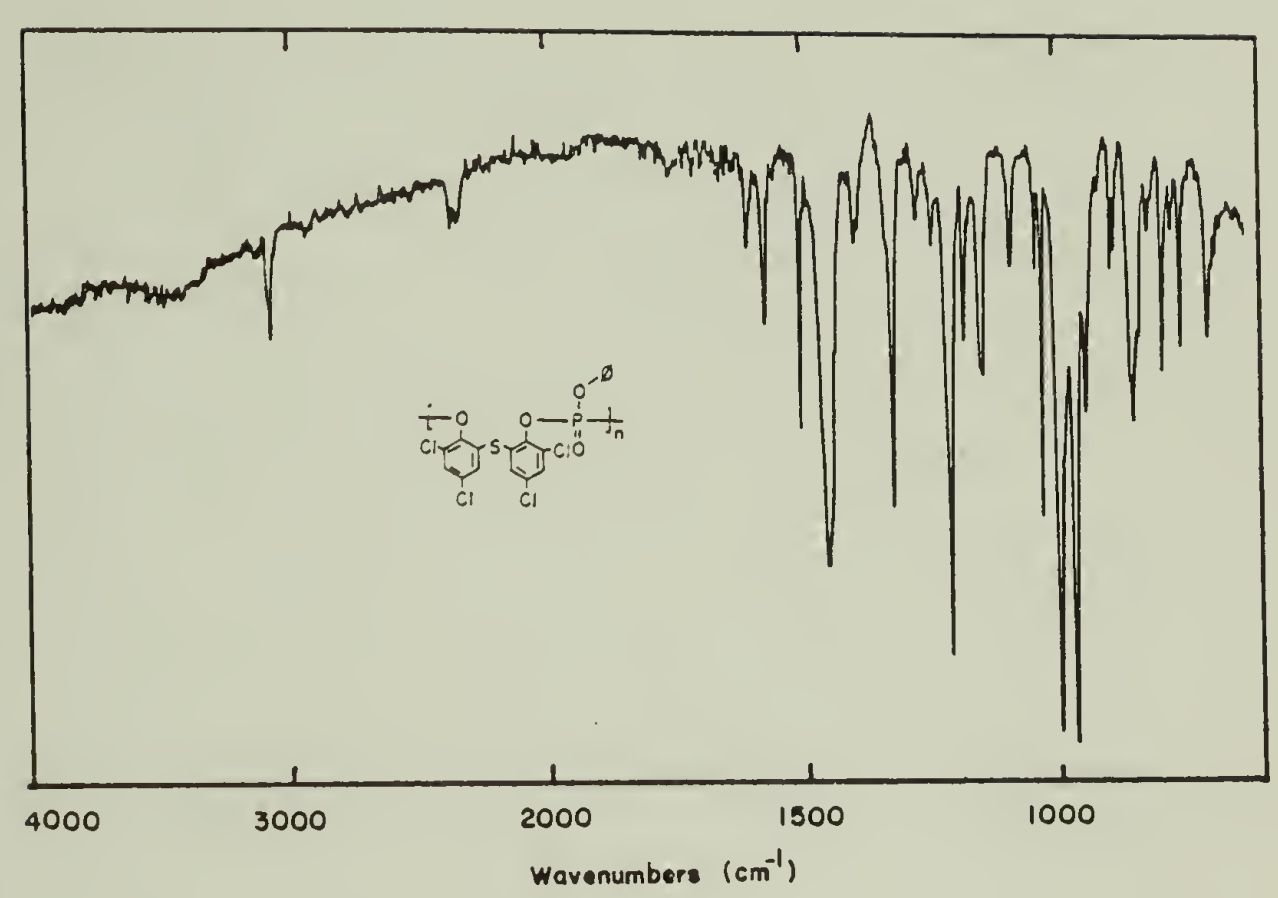
Wavenumbers (cm⁻¹)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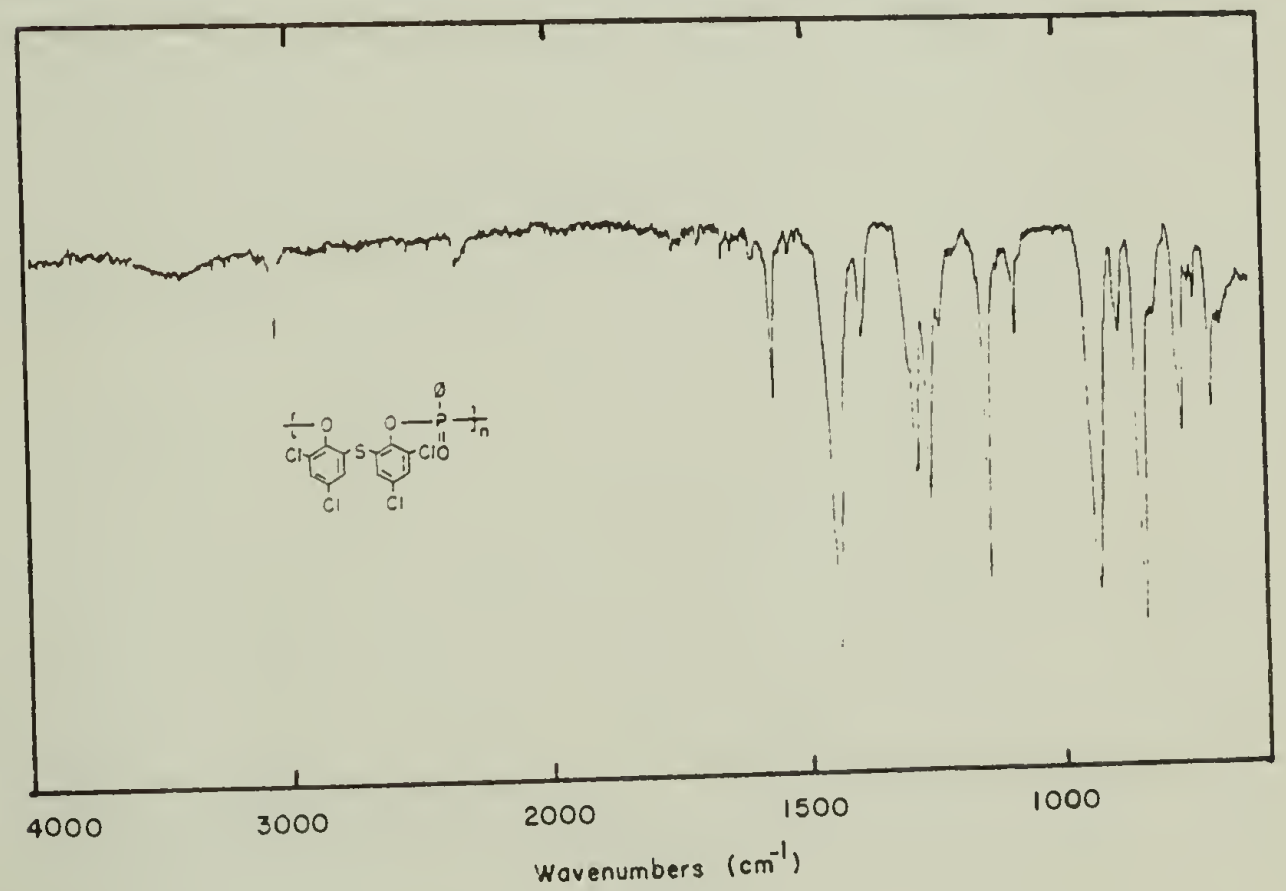
Wavenumbers (cm⁻¹)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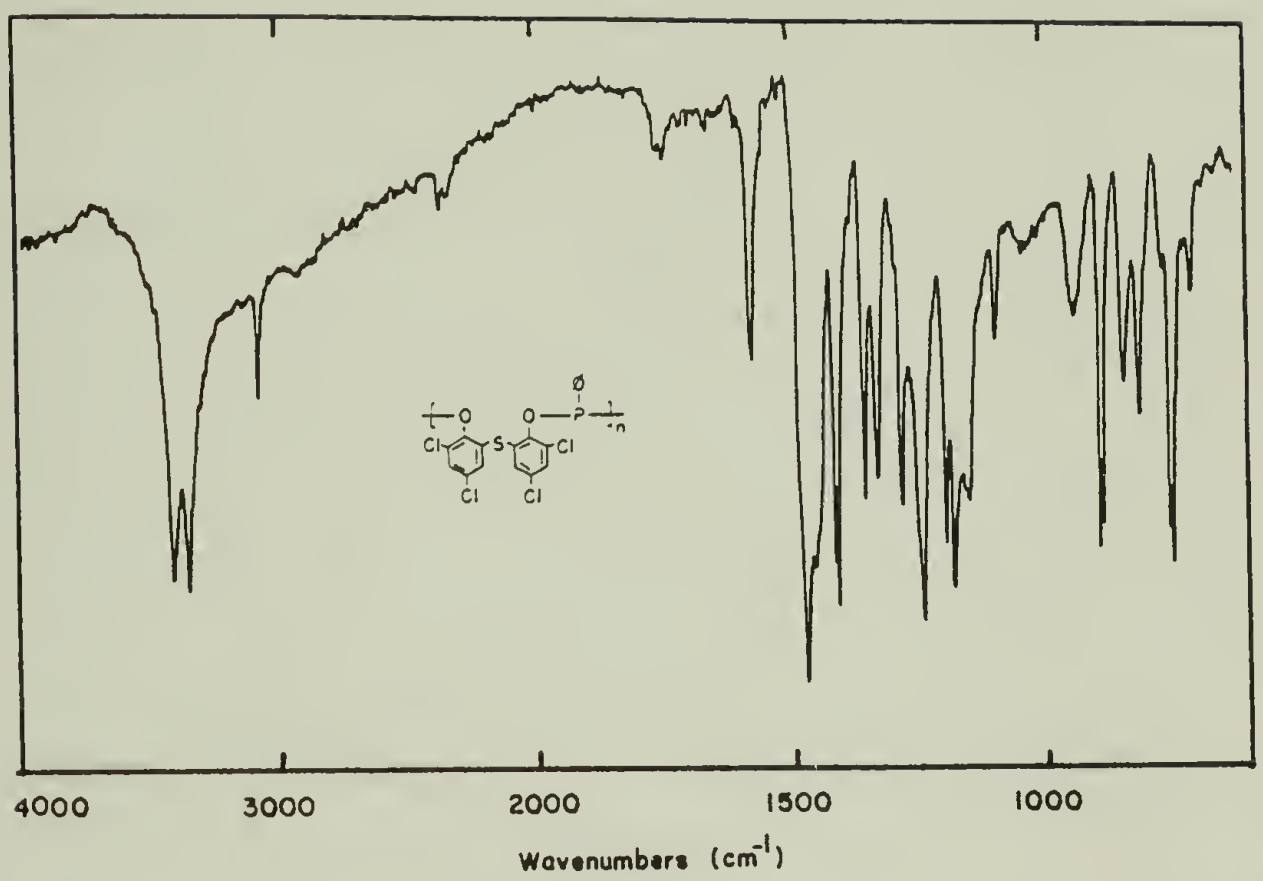
Wavenumbers (cm⁻¹)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Wavenumbers (cm⁻¹)