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### Functional Polymers. X. Hydrolysis Studies of Polyesters and Polycarbonates of Bithionol and Their Copolymers

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## Functional Polymers. X.\* Hydrolysis Studies of Polyesters and Polycarbonates of Bithionol and Their Copolymers

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### ABSTRACT

The hydrolysis behavior of a number of polymers of bithionol [2,2'-thiobis(4,6-dichlorophenol)] was investigated. The hydrolysis of polyesters of bithionol with aliphatic or aromatic dicarboxylic acids or phosphorus acids as well as polycarbonates and alternating copolycarbonates and polyurethanes or co(polycarbonates/polyurethanes) depends primarily on the water solubility of the polymer or at least on its degree of swelling. In the most favorable case of the alternating bithionol/PEG 4000 copolycarbonate the hydrolysis rate of the polymer at 37°C was 1.62 L/mol/min at pH 10, 0.63 L/mol/min at pH 4 and 0.17 L/mol/min at pH 7.4. Copolycarbonates and copolyurethanes with PEG 4000 in the polymer chain have slightly lower rates of hydrolysis. When the solubility of the polymer is low and the crystallinity

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<sup>†</sup>Deceased, February 16, 1981.

is high, the rate of hydrolysis of the polymer decreases by several orders of magnitude.

## INTRODUCTION

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].

The majority of work in the area of polymer drug systems has concentrated on the sustained delivery of drugs at optimal rates and on the release of herbicides and insecticides with minimal effect 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, bioactive compounds or drugs are conventionally dispensed at periodic intervals. This is necessary in order to maintain the concentration of bioactive 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 bioactive 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.

In order to chemically combine compounds with polymers, the required biologically active agent, or drug, may be complexed [16, 17] or bonded ionically [12, 18-21] or covalently [6, 12, 13] with a variety of macromolecular substances.

Active pharmaceutical agents can be covalently bonded to polymers in one of several ways. Polymers with active agents covalently bound as side chains or pendant groups can be prepared through either (1) polymerization of functional monomers or (2) reactions on polymers. Both methods have been utilized to give different materials with properties useful for a variety of applications [22, 23].

Covalently bonded drugs of this type 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. Polymeric antifungal compounds, for example, have been made by grafting the active antifungal agent pentachlorophenol onto ligno-cellulose fibers [24]. Fungal attack on the system probably releases the pentachlorophenol from the polymer backbone, thus providing the antifungal activity observed.

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 incorporation of active agents into the backbone of a polymer chain has been discussed in our earlier papers [25-27]. Although relatively few polymeric pharmaceuticals of this type have been prepared, a number of advances have been made, many of which show considerable promise [28-31].

One of the major mechanisms of polymer degradation in physiological systems is hydrolysis. Consequently, 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 of sustained action polymeric pharmaceuticals. 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 [12, 32, 34].

Although there is a considerable 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 [35] examined the alkaline hydrolysis of poly(ethylene terephthalate) (PET); however, he did so at only one pH level (alkali concentration). Rudakova et al. [36], 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 8.2-39.2%. 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.

The acid hydrolysis of polyesters catalyzed with hydrochloric acid and p-toluenesulfonic [37] 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 polymer chain. Ether oxygens in the glycol portions of the polyester chain (diethylene glycol in particular) enhanced the rate of hydrolysis almost two-fold. The rate was considerably reduced in the case of the sterically hindered polyesters 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 [38] and alkaline hydrolyses [39] determined in earlier studies.

The hydrolysis of linear polyesters [40] 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 [37].

A number of studies devoted to examining the hydrolysis of polycarbonates have been carried out [41]. 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 [42-49]. All the authors agreed that N-substituted carbamates were more stable to hydrolysis than the unsubstituted derivatives.

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, can be substituted to give not only triesters but also di- and monosubstituted esters as well. Much of the literature concerning the hydrolysis of phosphate esters has been extensively reviewed [50].

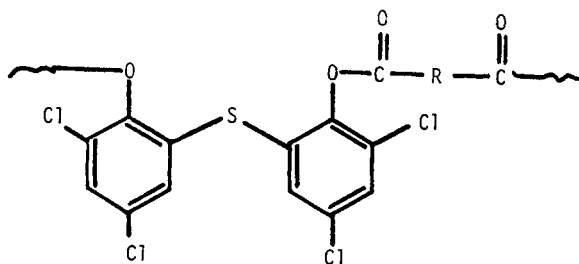
Metal ions have also been shown to influence the hydrolysis of phosphate esters. Murakami and Sunamoto [51] have postulated that this influence results from an effective charge neutralization of the substrate. They also found that chelate-forming ability is one of the most important factors for the catalytic efficiency of bivalent metal ions, such as  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ , and  $\text{Mg}^{2+}$ . The presence of specific metal ions, particularly  $\text{Mg}^{2+}$ , in many biological reactions involving phosphates is of great importance. Many hydrolysis reactions will not proceed in the absence of  $\text{Mg}^{2+}$ . This has been demonstrated in the phosphorylation of glucose with adenosine triphosphate (ATP), for example [52]. The actual substrate is thought to be the  $\text{Mg}^{2+}$ -chelate of ATP.

It was the objective of this work to study the hydrolysis, under conditions resembling those encountered in physiological systems, of polyesters, polycarbonates, copolycarbonates, polyurethanes, and copolyurethanes which have 2,2'-thiobis(4,6-dichlorophenol) (bithionol) in the backbone and evaluate those chemical and physical factors that affect the subsequent role of degradation.

## EXPERIMENTAL

### Materials

The synthesis and characterization of the polyesters, polycarbonates, (Eq. 1) polyurethanes, (Eq. 2), copolycarbonates, and various polymers from phosphorus acids were described in two previous papers [26, 27]. (Eq. 3).

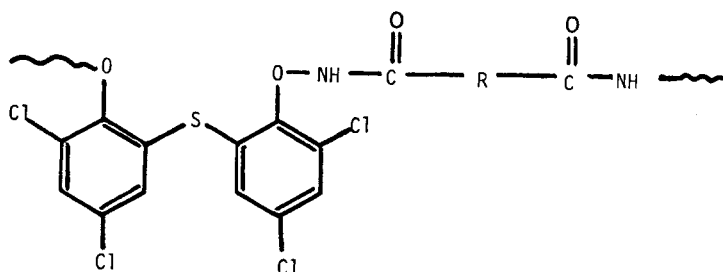


(1)

$$R = -(CH_2)_n, n = 1, 2, 4, 8$$

$$-C_6H_4, m-, p-$$

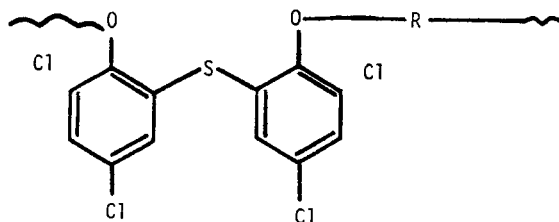
$$-(O-CH_2-CH_2)_n-O-, n = 1 \text{ to } \sim 100$$

$$MW = 62 \text{ to } \sim 4000$$


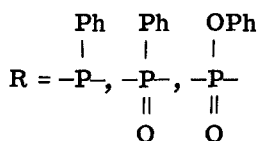
(2)

$$R = -(CH_2)_n, n = 2, 3, 4, 6, 10$$

$$-C_6H_4, m-, p-$$

$$-C_6H_4-CH_2-C_6H_4-$$


(3)



## Measurement of the Rates of Hydrolysis of Bithionol Polymers

### Preparation of Buffer Solutions

1. pH 4.0 buffer. Potassium biphthalate (2.55 g, 12.5 mmol) was dissolved in distilled water to make a 250-mL solution.

2. pH 10.0 buffer. Sodium bicarbonate (0.86 g, 10.3 mmol) and 0.1007 M aqueous sodium hydroxide (43.8 mL) were dissolved in water to make a 250-mL solution.

3. pH 7.4 buffer. Monobasic potassium phosphate (4.73 g, 34.8 mmol) and dibasic sodium phosphate (17.28 g, 121.7 mmol) were dissolved in water to make a 400-mL solution.

### Preparation of Polymer Solutions

Volumetric flasks (100 mL) were charged with powdered polymer and buffer solution and the resultant mixtures were stirred for 24 h. The flasks were then brought to volume with additional buffer solution.

### 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 actual weight of the polymers was obtained.

### Preparation of Bithionol Absorption 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 absorption of each of these solutions was then measured at 318.0 nm using a 1-cm quartz cuvette.

### Measurement of the Rate of Release of Bithionol from Polymer Solutions

The aqueous solutions prepared above were immersed in a constant temperature bath held at  $37.0 \pm 0.2^\circ\text{C}$ . At periodic intervals aliquots were removed from each, diluted as necessary with buffer solution (pH 10.0), and the UV absorbance at 318.0 nm measured using a 1-cm quartz cuvette.

The solubility of all polyesters, polyurethanes, and copolycarbonates was determined at pH 7.4 aqueous solution to be less than 0.01%. Bithionol/PEG 4000 alternating copolycarbonate and bithionol/1,10-decanediol/PEG 4000 terpolycarbonate was soluble to  $> 3$  g/100 mL.

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

## RESULTS AND DISCUSSION

We have studied the hydrolysis rate of bithionol-containing polymers, polyesters, polyurethanes, and polyphosphates at 37°C and a buffered aqueous solution of a pH of 7.4 over several weeks and found that a hydrolysis rate of up to 1.0%/d could be achieved under the most favorable conditions. The limiting factor for the hydrolysis of these polymers is their solubility.

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, provided 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 the polymers studied, absorbs very strongly at 318 nm in the UV region of the spectrum, allowing it to be detected at concentrations as low as  $10^{-6}$  mol/L. 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 absorption of UV light at 318 nm as a function of bithionol is shown in Fig. 1. It can be seen that the absorbance is linear over the range of concentrations examined, yielding a molar extinction coefficient of  $1.58 \times 10^4$  L/mol cm.

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 h 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:



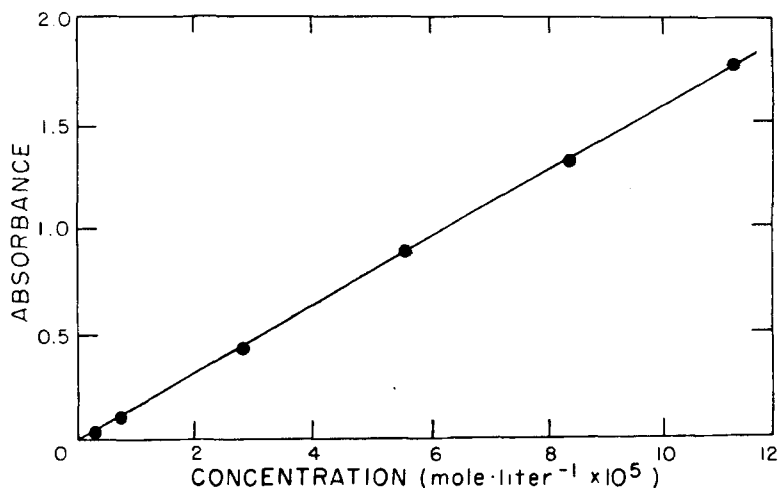


FIG. 1. Absorbance of bithionol as a function of concentration.

$$A = \epsilon bc$$

where  $A$  is the absorbance of the solution,  $\epsilon$  is the molar extinction coefficient or molar absorptivity expressed in  $L/mol\ cm$ ,  $c$  is the concentration in  $mol/L$ , and  $b$  is the path length of solution.

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 found to be completely water soluble (Eq. 1). 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 Fig. 2. 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 nonzero-order reaction kinetics. Assuming second-order kinetics, rate constants for the hydrolyses can be obtained using the following kinetic equation developed by Szabo-Rethy and Vancso-Szmercsanyi [37]:

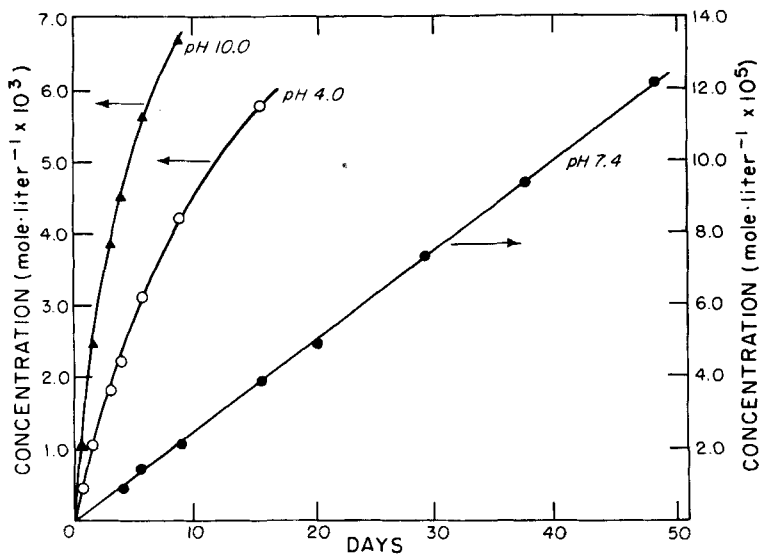


FIG. 2. Concentration of bithionol released from bithionol/PEG 4000 alternating copolycarbonate as a function of time. 37°C.

$$\ln \frac{E_0}{E_0 - x} = kct$$

where  $E_0$  is the initial concentration of ester or urethane groups in mol/L,  $x$  is the concentration of bithionol produced by the hydrolysis during a period of  $t$  days in mol/L,  $k$  is the rate constant of the reaction in L/mol d, and  $c$  is the concentration of catalyst in mol/L.

The validity of the assumption was verified by the experimental results shown graphically in Fig. 3. The calculated second-order rate constants are shown in Table 1. 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 2 times as rapid.

Both the water-soluble and the water-swelling polymers showed similar kinetic behavior in neutral solution as shown in Figs. 4 and 5. The calculated rate constants are compared in Table 2. 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 a profound influence on the rate of hydrolysis. This phenomenon is similar to that observed in 1972 by Szabo-Rethy and Vancso-Szmercsanyi [37] who found that although the rate of hydrolysis of polyesters obtained from aliphatic

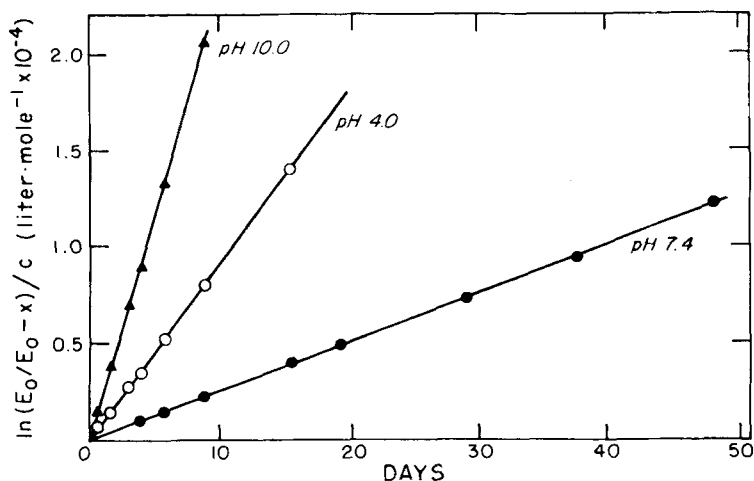


FIG. 3.  $(\ln(E_0/E_0 - x)/c)$  as a function of time for bithionol/PEG 4000 alternating copolycarbonate. 37°C.

TABLE 1. Effect of pH on the Rate Constant of the Hydrolysis of Bithionol/PEG 4000 Alternating Copolycarbonate in Aqueous Solution at 37°C

pH	k (L/mol min)
4.0	0.626
7.4	0.173
10.0	1.625

saturated dicarboxylic acids was independent of the chain 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. Although 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

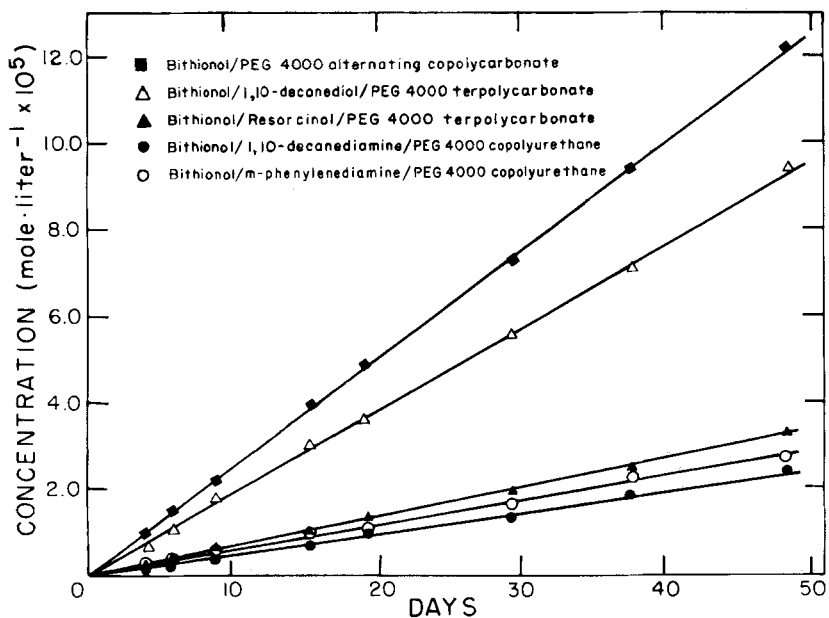


FIG. 4. Concentration of bithionol released from water-soluble and swellable bithionol polymers as a function of time. pH 7.4. 37°C.

Rudakova [36] 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 equation

$$k = \frac{dA}{dt} \frac{V}{\epsilon \ell}$$

where  $V$  is the volume of solution,  $A$  and  $\epsilon$  are the absorbance and molar extinction coefficient of the monomer species, respectively, and  $\ell$  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 3. 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 the reaction as:

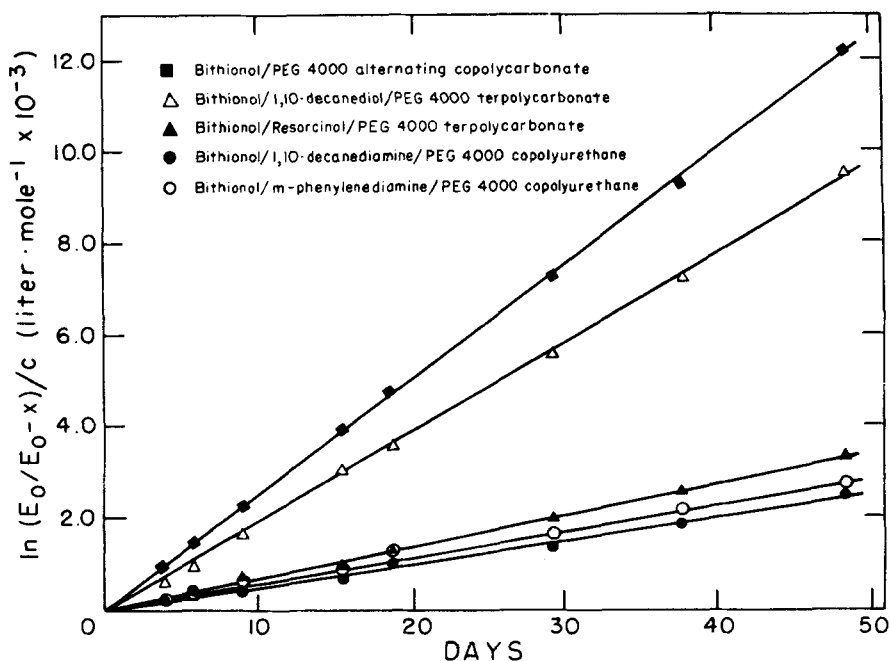


FIG. 5.  $(\ln (E_0/E_0 - x)/c)$  as a function of time for water-soluble and swellable bithionol polymers. pH 7.4. 37°C.

TABLE 2. Rate Constants of the Hydrolysis of Water-Soluble Polymers in Aqueous Solution at 37°C, pH 7.4

Polymer	$k \times 10^2$ (L/mol min)	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 <sup>a</sup>	4.7	30
Bithionol/1,10-decanediamine/ PEG 4000 copolyurethane <sup>a</sup>	3.5	22
Bithionol/m-phenylenediamine/ PEG 4000 copolyurethane	4.0	25

<sup>a</sup>Water swellable.

TABLE 3. Reaction Rate Constants of the Hydrolysis of Water-Insoluble Bithionol Polymers at 37°C, pH 7.4

Polymer	$k \times 10^{12}$ (mol/min)
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 isophthalate)	1
Poly(bithionol phenylphosphate)	5
Poly(bithionol phenylphosphonate)	2
Poly(bithionol phenylphosphinate)	2

$$\text{Rate} = \frac{d[A]}{dt} = k[\text{polymer}][\text{H}_2\text{O}]$$

where  $d[A]/dt$  is the concentration of monomer released per unit time, measured spectrophotometrically,  $k$  is the reaction rate constant, and  $[\text{polymer}]$  and  $[\text{H}_2\text{O}]$  are the concentrations of polymer and water, respectively. Since water was present in great excess, its concentration was 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.

The presence of divalent metals ions,  $\text{Mg}^{2+}$  in particular, has a great influence on a number of reactions involving phosphates and phosphate esters. Consequently, the effect of 0.001 M concentration of  $\text{Mg}^{2+}$  (approximately that encountered in physiological systems) on the rate of hydrolysis of bithionol polymers containing phosphorus in the backbone was investigated. Magnesium, in the form of  $\text{MgSO}_4$ , 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 4).

TABLE 4. Effect of Added  $Mg^{2+}$  on the Rate Constants of the Hydrolysis of Bithionol Polymers Containing Phosphorus at 37°C, pH 7.4

Polymer	$k \times 10^{12}$ (mol/min)
Poly(bithionol phenylphosphate)	5
Poly(bithionol phenylphosphonate)	2
Poly(bithionol phenylphosphinate)	2
Poly(bithionol phenylphosphate) + 0.001 <u>M</u> $Mg^2$	7
Poly(bithionol phenylphosphonate) + 0.001 <u>M</u> $Mg^2$	2
Poly(bithionol phenylphosphinate) + 0.001 <u>M</u> $Mg^2$	2

The objectives of the project were 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. These objectives were 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 was 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 was 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.

#### ACKNOWLEDGMENTS

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