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Hydrolysis of Some Poly(*ortho*-ester)s in Homogeneous Solutions

TUE HUU NGUYEN *, CHUNG SHIH[§], KENNETH J. HIMMELSTEIN *[§‡x], and TAKERU HIGUCHI *[§]

Received November 14, 1983, from the **Departments of Pharmaceutical Chemistry and* [‡]*Chemical and Petroleum Engineering, The University of Kansas, Lawrence, KS 66045* and [§]*INTER$_x$ Research Corp., Merck Sharp & Dohme Research Laboratories, Lawrence, KS 66044.* Accepted for publication January 13, 1984.

Abstract □ The hydrolysis of poly(*ortho*-ester)s and a monomeric model compound, 3,9-dibenzyloxy-3,9-diethyl-2,4,8,10-tetraoxaspiro[5,5]undecane, was carried out in dioxane-d_8–dioxane and followed by ^{1}H-NMR and HPLC, respectively. Experimental results suggested that the polymer degradation proceeds to a large extent *via* random scission. The hydrolysis was catalyzed by the acid; the catalytic rate constant increased predictably with decreasing aqueous pK_a of the acid. The reaction is first order with respect to the catalyst concentration and the number of *ortho*-ester linkages present, and it is independent of water in the concentration range studied. Strain at the *ortho*-ester bond may be a factor influencing the hydrolysis rate.

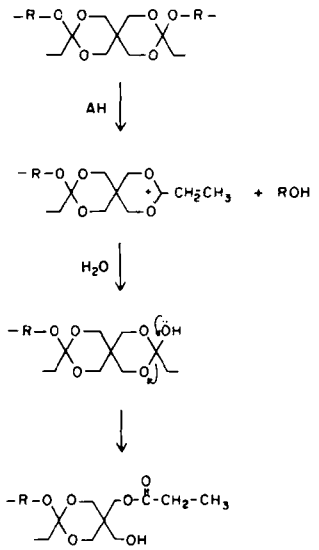
Keyphrases □ Hydrolysis—poly(*ortho*-ester)s, homogeneous solutions □ Polymers—hydrolysis of poly(*ortho*-ester)s, homogeneous solutions □ Degradation—polymers, hydrolysis of poly(*ortho*-ester)s, homogeneous solutions □ Poly(*ortho*-ester)s—hydrolysis, homogeneous solutions

Poly(*ortho*-ester)s are a novel class of polymers with potential utility in drug delivery systems. Their use as an erodible matrix for the delivery of a steroid has been demonstrated by Heller *et al.* (1). In these systems, water-soluble salts were incorporated into the polymer, and the release mechanism appeared to be similar in part to that described by Fedors (2). Osmotic imbibition of water induced the swelling of the matrix, which subsequently burst and released the drug.

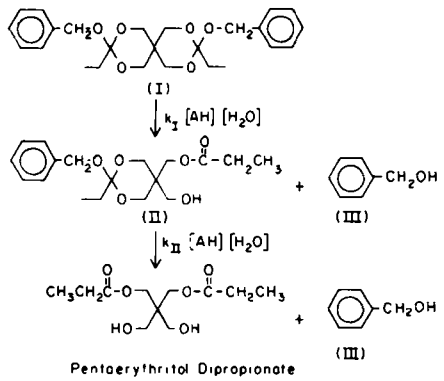
Poly(*ortho*-ester)s, as with most *ortho*-esters, undergo acid-catalyzed hydrolysis quite readily and are relatively unreactive in neutral or basic media (3, 4). Thus, when exposed to an aqueous environment, the erosion of the polymeric matrix may be induced by the presence of an acidic catalyst. The acid may be external or may be generated *in situ* by an acid-producing agent such as acid anhydride incorporated in the device. Since acid anhydrides are neutral, and therefore noncatalytic, they add to the stability of the device during storage.

Following this rationale Shih *et al.* (5) have demonstrated the use of poly(*ortho*-ester)s delivery systems, achieving zero-order release of timolol maleate. The release rate was effectively controlled by the amount of acid anhydride incorporated into the device and the aqueous pK_a of the corresponding acid. It was proposed that the mechanism of drug release from such a system results from the contribution of several processes, namely, the permeation of water into the polymer matrix, the hydrolysis of the acid anhydride to the corresponding acid, the hydrolysis of the *ortho*-ester linkages, and the dissolution of the drug species into the medium (5).

The present studies were undertaken as part of an effort to understand the various physicochemical processes which govern the release of drugs from poly(*ortho*-ester)s delivery systems. In an attempt to separate the various contributing factors, we report the kinetics of the hydrolysis of poly(*ortho*-ester)s [poly(3,9-dialkyloxy-3,9-diethyl-2,4,8,10-



*Scheme I—Acid-catalyzed hydrolysis of poly(*ortho*-ester)s.*



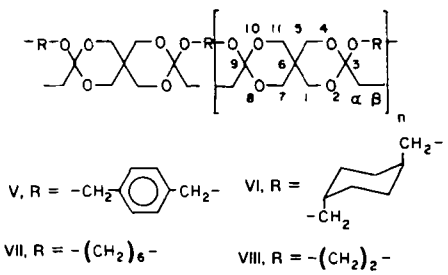
Scheme II—Acid-catalyzed hydrolysis of 3,9-dibenzyloxy-3,9-diethyl-2,4,8,10-tetraoxaspiro[5,5]undecane.

tetraoxaspiro[5,5]undecane)] and a monomeric model compound, 3,9-dibenzyloxy-3,9-diethyl-2,4,8,10-tetraoxaspiro[5,5]undecane (I) in homogeneous solutions. From this experiment, the intrinsic reactivity of the polymers may be independently obtained. The mode of depolymerization, the reaction rate constants, and the sensitivity of the reaction to the nature of the catalysts and to the concentration of water and acid were determined.

Several papers and reviews on *ortho*-ester chemistry have been published (3, 4, 6–11). The acid-catalyzed hydrolyses of *ortho*-esters is now thought to proceed *via* three steps. The first, and generally the rate-determining, step is the generation of a dialkoxycarbonium ion and an alcohol. The carbonium ion hydrates readily in the second step to form an unstable intermediate, the hydrogen *ortho*-ester, which breaks down to give an ester and an alcohol. For cyclic *ortho*-esters, the exocyclic alkoxy group is normally expelled in the first stage (11). Accordingly, the acid-catalyzed hydrolysis of I and poly(*ortho*-ester)s may be described as shown in Schemes I and II. The final products, alcohol and pentaerythritol dipropionate, were isolated and identified by HPLC comparison with authentic samples.

EXPERIMENTAL SECTION

Materials—Compound I and all polymers were used as provided[1]. Compound I was further purified by preparative TLC with precoated silica-gel glass plate[2]. The solvent system was 5% v/v ethyl acetate[3] in hexane[3]. The band at R_f 0.89 was located under short-wavelength UV light, removed from the plate, and extracted with methylene chloride[3]. The solvent was evaporated with a commercial evaporator[4], and the residual solvent was removed under reduced pressure at room temperature for 12 h. Water was distilled in an all-glass apparatus. Dioxane[3] was dried with lithium aluminum hydride[5] and distilled. Acetonitrile[3], HPLC grade, dioxane-d_8[6], trichloroacetic acid[6], dichloroacetic acid[6], monochloroacetic acid[6], formic acid[6], phthalic acid[6], and maleic acid[6] were used as received.



[1] Provided by Dr. J. Heller, SRI International, Menlo Park, Calif.
[2] Precoated silica gel GF 1500-μm glass plate; Analtech, Inc., Newark, Del.
[3] Fisher Scientific Co., Fair Lawn, N.J.
[4] Rotavapor; Brinkman Instruments, Westbury, N.Y.
[5] Alfa Products, Danvers, Mass.
[6] Aldrich Chemical Co., Inc., Milwaukee, Wis.

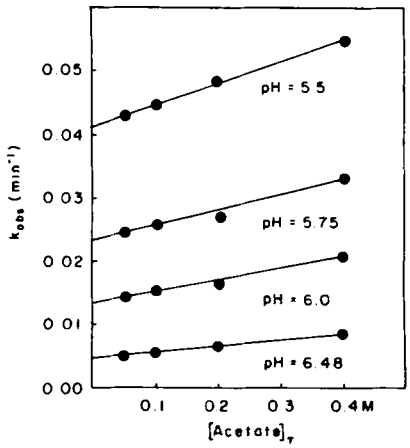


Figure 1—*Buffer-catalyzed hydrolysis of I in dioxane–water (50:50, v/v) at 25°C; μ = 0.5 M with KCl. Plot of the observed rate constant* versus *total buffer concentration.*

Methods—The hydrolysis of I was conducted both in 50% v/v buffered dioxane–water solutions and in pure dioxane. Samples of I were accurately weighed into 5-mL volumetric flasks and dissolved in 4 mL of dioxane. To start the experiment, measured amounts of water and acid stock solution in dioxane were transferred to the flask, and the volumes were brought to 5 mL with dioxane. The initial concentration of I was 0.01 M. In experiments in buffered solutions, 100 μL of a stock solution of I in dioxane was injected directly into 4 mL of buffered solution; the volume was then made up to 5 mL with the same solution resulting in an initial 0.02 M concentration of I. The flasks were stoppered and sealed[7] and then placed in a water bath. The reaction was monitored by following the disappearance of I and the appearance of benzyl alcohol (III) by HPLC. The mobile phase consisted of 20% v/v acetonitrile–water for III and 80% v/v acetonitrile–water for I. The flow rate was 2 mL/min, and the detector was set at 254 nm. The column employed was an ultrasphere-octadecysilane[8].

A series of four poly(*ortho*-ester)s, the structures of which are shown, was chosen for the study. Accurately weighed amounts of polymer were dissolved in dioxane-d_9. A total of 400 μL of the solution was transferred into ^{1}H-NMR sample tubes[9]. Immediately before the experiment, measured quantities of water and stock solution of acid in dioxane-d_8 were injected into the tube. The total volume was brought to 500 μL with dioxane-d_8 and mixed. The resulting concentration of polymer was 8% w/v. The sample tubes were then sealed and placed in a water bath at 37°C. Readings were performed periodically on a ^{1}H-NMR spectrometer[10].

For the condensation copolymer of 3,9-bis(ethylidene)-2,4,8,10-tetraoxaspiro[5,5]undecane (IV) and 1,4-benzenedimethanol (V), monitoring of the disappearance of the peaks at δ = 1.8 ppm corresponding to the α methylene group or the appearance of the methylene group α to the carbonyl carbon of the degraded product at δ = 2.3 ppm gives a direct account of the rate of bond

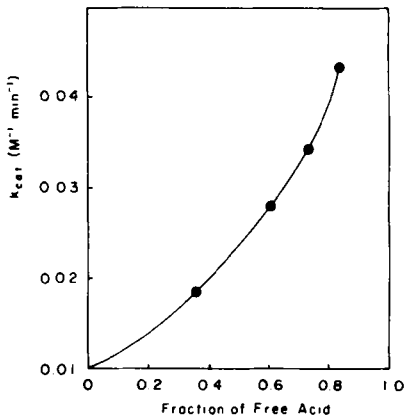


Figure 2—*Buffer-catalyzed hydrolysis of I in dioxane–water (50:50, v/v) at 25°C; μ = 0.5 M with KCl. Plot of the rate constant of the general acid-catalyzed reaction* versus *the fraction of free acetic acid.*

[7] Parafilm.
[8] Altex, Berkeley, Calif.
[9] Kontes Glass Co., Vineland, N.J.
[10] Model T60; Varian Instrument Co., Palo Alto, Calif.

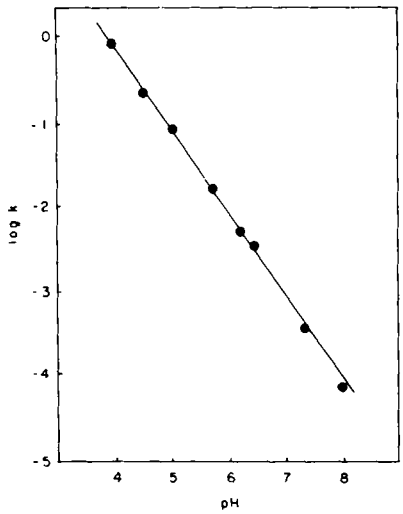


Figure 3—*Hydrolysis of I in dioxane-water (50:50) at 25°C; μ = 0.1 M with KCl. Plot of the logarithm of the observed rate constant at zero buffer concentration* versus *pH.*

cleavage. Only the appearance of the quartet at δ = 2.3 ppm can be used in the cases of the condensation copolymers of IV and diols such as 1,4-*trans*-cyclohexanedimethanol (VI) and 1,6-hexanediol (VII) due to interference of other protons in the system.

RESULTS AND DISCUSSION

pH-Rate Profile—The hydrolysis of I was carried out in 50% v/v buffered dioxane-water solutions at 25°C. The use of mixed solvent rendered the interpretation of the pH determination[11] somewhat difficult. However, when the apparent pH in the 50% v/v dioxane-water solvent system was plotted against the pH of the aqueous buffered solutions, prepared similarly but without dioxane, a straight line was obtained with a zero-intercept and a slope of 1.05. This seems to suggest that the changes in the pH-meter readings were proportional to the changes in the hydronium ion activity in this system. The pH range studied was from 4 to 8. The buffer concentration was varied from 0.4 to 0.005 M, whereas the ionic strength was kept at 0.1 or 0.5 M with KCl. It was assumed that the salts employed were fully ionized. The loss of I was followed by HPLC and found to follow pseudo-first-order kinetics. The effect of acetate buffer concentration on the reaction rate is illustrated in Fig. 1. The observed rate constant seems to increase linearly with buffer concentration. The slope of the lines increases with decreasing pH, suggesting that the free acid is the catalytic species. However, a plot of the rate constants of the general acid-catalyzed reaction against the fraction of free acid (Fig. 2) did not yield a straight line as expected. A change in the activity coefficient of the free acid and the anion at high buffer concentrations may be a possible explanation. The pK_a of acetic acid under the reaction conditions was determined to be 6.22 by pH titration.

The rate constants extrapolated to zero buffer concentration were employed to construct the pH-rate profile. As evident from the linearity of the plot of

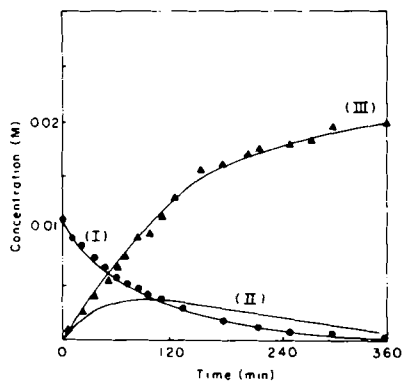


Figure 4—*Hydrolysis of I in dioxane at 37°C; water, 2 M; maleic acid, 1.25 × 10⁻³ M. Plot of the concentration of different species* versus *time. Points are experimental data; solid lines are generated from the kinetic model.*

[11] Accumet model 610A; Fisher Scientific Co.

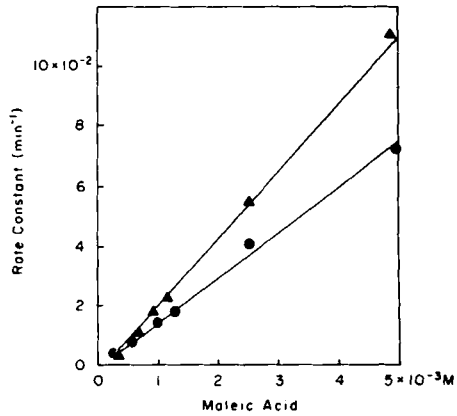


Figure 5—*Hydrolysis of I in dioxane at 37°C; water, 2 M. Plot of the two consecutive rate constants* versus *maleic acid concentration. Key: (▲) k_{II}; (●) k_I.*

the logarithm of the pseudo-first-order rate constant extrapolated to zero buffer concentration *versus* pH with a slope of −1 (Fig. 3), hydronium ions appear to be the catalyst in this pH range. The reaction was also studied at pH 13. No noticeable degradation could be detected. The value for the specific acid-catalyzed reaction (k_{H^+}) was obtained from the intercept of the line with the ordinate. A k_{H^+} value of 1.03×10^4 min^{-1} M^{-1} at μ = 0.1 M was only slightly smaller than the k_{H^+} of 1.09×10^4 min^{-1} M^{-1} at μ = 0.5 M, suggesting that the effect of the salt was not significant.

Mode of Depolymerization—There are two types of linkages involved, the internal linkages and those at the end of the polymer chain. Differentiation of their reactivity directly from the polymer molecules is difficult. However, I has two *ortho*-ester linkages. When they are intact, the bonds are similar to the internal bonds. When one bond is broken, the remaining one resembles the one at the end of the chain. Thus, according to Scheme II, it is possible to determine the relative reactivity of those two types of bonds by comparing the rate of disappearance of I and the monoester (II), its partially degraded product.

The reaction was carried out in dioxane at 37°C. The concentrations of I and water were 0.01 and 2 M, respectively. The maleic acid concentration was varied from 2.5×10^{-4} to 5×10^{-3} M. The loss of I and the formation of III were followed by HPLC.

The differential equations defining the kinetic system are:

$$\frac{-d[I]}{dt} = k_I [I] \qquad \text{(Eq. 1)}$$

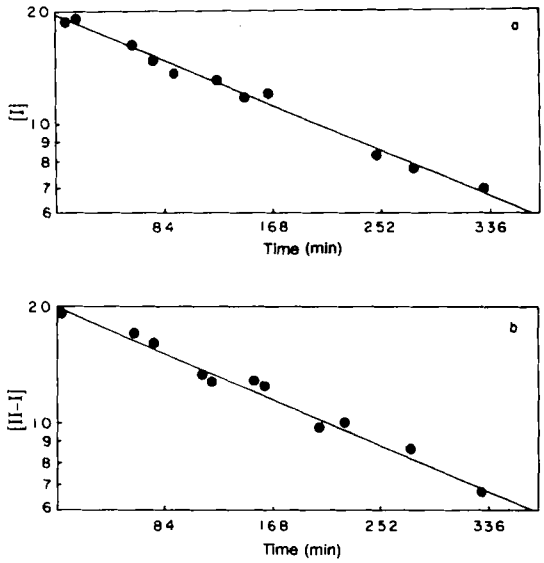


Figure 6—*Hydrolysis of the IV-V copolymer in dioxane-d_8 at 37°C; water, 2 M; trichloroacetic acid, 1.25 × 10⁻³ M. Plot of logarithm of peak integration* versus *time. [I], integration of NMR peaks during the reaction; [II], integration of peaks when the reaction is completed. Key: (a) disappearance of the α-methylene protons in the polymer; (b) appearance of methylene protons α to the carbonyl carbon in the degradation product.*

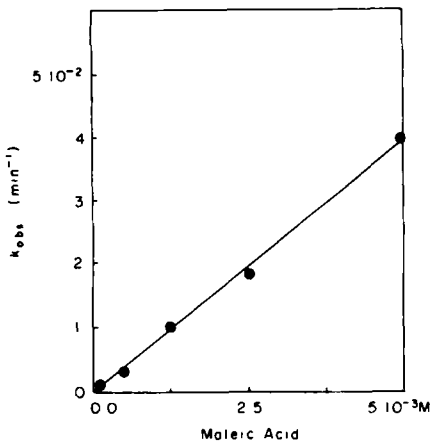


Figure 7—*Hydrolysis of I in dioxane at 37°C; water, 2 M. Plot of the observed rate constant* versus *maleic acid concentration.*

$$\frac{d[II]}{dt} = k_I [I] - k_{II} [II] \quad \text{(Eq. 2)}$$

$$\frac{d[III]}{dt} = k_I [I] + k_{II} [II] \quad \text{(Eq. 3)}$$

At $t = 0$, $[I] = [I]_0$, which is the initial concentration of I, and $[II] = [III] = 0$.

The estimation of k_I and k_{II}, the apparent pseudo-first-order rate constants for the two consecutive steps, respectively, was performed on a computer[12] by a nonlinear regression program based on a pattern-search algorithm. Typical experimental data and the fitted curves generated for the reaction from the kinetic model above are shown in Fig. 4.

The constants k_I and k_{II} obtained for various maleic acid concentrations are plotted in Fig. 5. The slope of the lines was taken to be the second-order rate constant for the reaction. The ratio k_{II}/k_I was ~1.55, suggesting that the bonds at the end of the chain are only slightly more reactive than the internal linkages.

In fig. 6, a semilogarithmic plot of the ^{1}H-NMR peak integration of the IV-V copolymer, as a function of time resulting from the hydrolysis in dioxane-d_8 at 37°C catalyzed by 2.55×10^{-3} M dichloroacetic acid, is shown. The water concentration was 2 M. The concentration of the IV-V copolymer was 8% w/v or ~0.23 M of the monomeric unit. Since each monomer has two *ortho*-ester linkages, the amount of water present was about five times that required for complete hydrolysis of the sample.

The pseudo-first-order rate constants for the disappearance of the methylene group and for the appearance of the methylene group α to the carbonyl carbon are 3.69×10^{-3} min^{-1} and 3.81×10^{-3} min^{-1}, respectively. This seems to validate the analytical procedure. The linear relationship suggests a random scission process in which the majority of the bonds are of equal accessibility

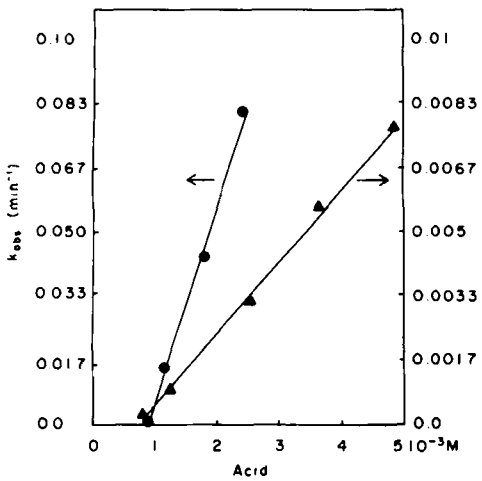


Figure 8—*Hydrolysis of the IV-V copolymer in dioxane-*d_8 *at 37°C; water, 2 M. Plot of the observed rate constant* versus *acid concentration. Key: (●) catalyzed by trichloroacetic acid; (▲) catalyzed by dichloroacetic acid.*

[12] Honeywell.

Table I—Second-Order Rate Constant for the Hydrolysis of I in Dioxane and the IV-V Copolymer in Dioxane-d_8 at 37°C[a]

Acid	Aqueous pK_a	k_2, M^{-1}·min^{-1}	
		I	IV-V Copolymer
Trichloroacetic acid	0.7	116.85	54.17
Dichloroacetic acid	1.48	4.65	1.99
Monochloroacetic acid	2.85	0.09	0.045
Formic acid	3.75		0.006
Maleic acid	1.83, 6.07	7.26	3.73
Phthalic acid	2.89, 5.51	0.47	

[a] The concentration of water was 2 M.

and the rate of scission is first order with respect to the number of *ortho*-ester linkages.

Effect of Acid Concentration and pK_a on the Hydrolysis of Poly(*ortho*-ester)s—The observed rate constant of the hydrolysis of I in dioxane at 37°C was plotted against the maleic acid concentration (Fig. 7). The reaction velocity of the IV-V copolymer in dioxane-d_8 at 37°C in the presence of different amounts of trichloroacetic acid and dichloroacetic acid is shown in Fig. 8. A linear relationship was apparent in all cases in the concentration range studied. The slope of the lines was taken as the second-order rate constant (k_2) of the reaction. The nonzero-intercept seen with the IV-V copolymer can be attributed to the presence of a small amount of alkaline impurities in the polymer.

The second-order rate constants for the hydrolytic reaction catalyzed by different acids are listed in Table I. A straight line can be drawn through the plot (Fig. 9) of log k_2 *versus* acid aqueous pK_a. A positive deviation was observed for the points corresponding to phthalic acid and maleic acid.

The unusually high acidity of the first dissociable proton of maleic acid (pK_{a_1}, 1.83), a diacid with its carboxylic groups in a *cis* position to each other, as compared with that of its *trans*-isomer, fumaric acid (pK_{a_1}, 3.03), was attributed to intramolecular hydrogen bonding which stabilizes the carboxylate monoanion. This interaction is further enhanced in an aprotic environment (12). Thus, it was not unexpected to see the deviation from a linear relationship found with the monoacid. A similar explanation should also hold true for phthalic acid, in which the second carboxyl group is in the *ortho*-position. The k_2 values for the hydrolysis of I are approximately twice that of the IV-V copolymer. The difference is probably due to the analytical methods employed. The degradation of I was monitored by following its disappearance by HPLC. Thus, the scission of one *ortho*-ester linkage results in the loss of one molecule of I. The NMR technique gives a true account of the rate of cleavage of the linkages. Statistically, it is expected that the rate constant of the disappearance of I should be approximately twice as fast as the rate of bond cleavage if the reactivity of the *ortho*-ester bond on the monomer and on the polymers is similar. This was further confirmed when

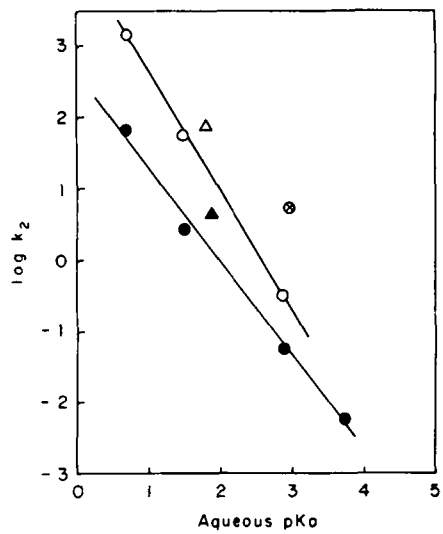


Figure 9—*Plot of the logarithm of the second-order rate constant* versus *aqueous* pK_a; *water, 2 M. The organic acids used were trichloroacetic acid (*pK_a, *0.70), dichloroacetic acid (*pK_a, *1.48), monochloroacetic acid (*pK_a, *2.85), formic acid (*pK_a, *3.75), Maleic acid (*pK_a, *1.83, 6.07) and phthalic acid (*pK_a, *2.89, 5.51). Key: hydrolysis of the IV-V copolymer in dioxane-*d_8 *at 37°C catalyzed by carboxylic monoacid (●), and by maleic acid (▲); hydrolysis of I in dioxane at 37°C catalyzed by carboxylic monoacid (○), by maleic acid (△), and by phthalic acid (⊗).*

Table II—Hydrolysis of I in Dioxane and the IV-V Copolymer in Dioxane-d_8 at 37°C [a]

Water Concentration, M	Dielectric Constant	Observed Rate Constant, min^{-1}	
		I [b]	IV-V Copolymer [c]
0.1	2.86		3.4×10^{-3}
0.5	5.37	1.63×10^{-2}	
1	8.34	1.72×10^{-2}	
2	13.73	1.97×10^{-2}	5.39×10^{-3}
3	18.52	2.23×10^{-2}	5.56×10^{-3}
4	22.80	2.56×10^{-2}	

[a] I, 0.01 M; IV-V copolymer, 8% w/v. [b] Reaction catalyzed by 2.5×10^{-3} M maleic acid. [c] Reaction catalyzed by 3.5×10^{-3} M dichloroacetic acid.

Table III—Hydrolysis of Poly(*ortho*-ester)s in Dioxane-d_8 at 37°C Catalyzed by Dichloroacetic Acid

Polymer	k_2, $M^{-1} \cdot min^{-1}$
IV-VI copolymer	0.87
IV-VII copolymer	1.80
IV-V copolymer	1.96
IV-VIII copolymer	2.81

k_2 values for the hydrolysis of I in dioxane at 37°C in the presence of maleic acid and 2 M water obtained by ^{1}H-NMR were compared with those obtained under the same conditions by HPLC. The ratio of k_2 HPLC-k_2 ^{1}H-NMR was 2.15.

Effect of Water Concentration on the Hydrolysis of Poly(*ortho*-ester)s—A semilogarithmic plot of the degradation of the 8% w/v IV-V copolymer in dioxane-d_8 at 37°C catalyzed by 3.5×10^{-3} M dichloroacetic acid in the presence of 0.1 M water is presented in Fig. 10. As expected, the reaction proceeded until ~25% of the *ortho*-ester linkages were cleaved. The initial slope was employed a the pseudo-first-order rate constant for the reaction. The observed rate constants for the reaction at different water concentrations are listed in Table II, along with the estimated dielectric constant of the dioxane-water system. These are computed from the dielectric constant of water of 78.54 (13) and from the dielectric constant for dioxane of 2.209 (13), assuming that the contribution of each component to the dielectric constant of the system is proportional to its mole fraction. The observed rate constant increases only 1.5-fold for a 30-fold increase in water concentration. A similar observation can be made for the hydrolysis of I in dioxane at 37°C catalyzed by 2.5×10^{-3} M maleic acid. When the rate constants were plotted (Fig. 11) against the solvent dielectric constant, an apparent linear relationship with a nonzero-intercept was observed. Thus, the experimental results suggest that, over the range studied, the reaction proceeds independently of the amount of water present, and the increase in reaction velocity is due to the change in polarity of the reaction medium. This is reasonable since the rate-determining step of the reaction is the formation of the dialkoxy carbonium ion which is independent of the water concentration.

Effect of Polymer Structure on the Hydrolysis Rate—The second-order rate constants for the hydrolysis of four polymers in dioxane-d_8 at 37°C catalyzed by dichloroacetic acid are shown in Table III. The polymers and water concentrations were held constant at 8% w/v and 2 M, respectively. Bunton and DeWolfe (7) have shown that an increase in the basicity of the oxygen atom on the leaving alkoxy group or a stabilization of the forming carbonium ion will result in a more reactive *ortho*-ester. For the polymers under consideration, once the alkoxy groups are cleaved, the resulting carbonium ions are identical; thus, if the observations of Bunton and DeWolfe are applicable, the difference in their reactivity should originate from the difference in the basicity

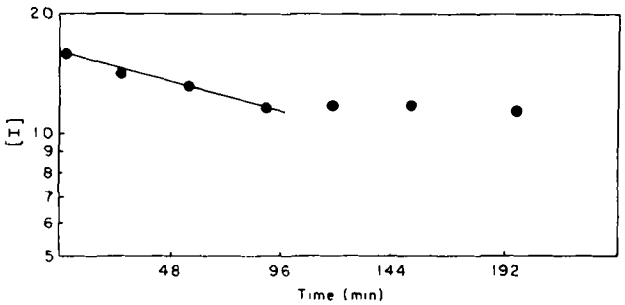


Figure 10—*Hydrolysis of the IV-V copolymer in dioxane-*d_8 *at 37°C; water, 0.1 M; polymer, 8.17% w/v; dichloroacetic acid, 3.5×10^{-3} M. [I], integration of NMR peaks during the reaction.*

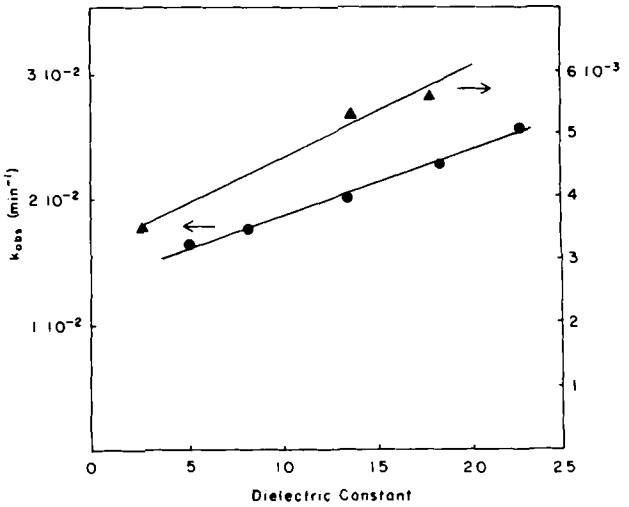


Figure 11—*Plot of the observed rate constant* versus *dielectric constant. Key (▲) hydrolysis of the IV-V copolymer in dioxane-*d_8 *catalyzed by 3.5×10^{-3} M dichloroacetic acid; (●) hydrolysis of I in dioxane at 37°C catalyzed by 2.5×10^{-3} M maleic acid.*

of the diol oxygen atoms. This would predict that IV-V and IV-ethylene glycol (VIII) copolymers are the most stable. The fact that the rank order of the second-order rate constant for the polymers studied cannot be rationalized in terms of the inductive effect of the diol alkyl chain on the basicity of the oxygen atoms at the reaction site implies that another driving force may be more influential. When the rate constants are compared with the molecular size of the diols, an apparent correlation is found. The smaller the diol molecule, the more reactive the polymer, suggesting that strain at the *ortho*-ester bond may be a factor determining the hydrolysis rate.

CONCLUSIONS

The hydrolysis of four poly(*ortho*-ester)s and a monomeric model compound in homogeneous solution was investigated. It appears that the reactivity of the *ortho*-ester linkage in the polymer chain is comparable to that of the linkage in the monomeric model compound. In 50% dioxane-water, the reaction is subject to both specific and general acid catalysis. In dioxane, the hydrolysis reaction is acid catalyzed and independent of the water concentration in the range studied. The rate equation for the hydrolysis of poly(*ortho*-ester)s in dioxane may be written as:

$$\frac{-d[n]}{dt} = k_2 [n] [AH] \qquad \text{(Eq. 4)}$$

where n is the concentration of *ortho*-ester linkage, AH is the concentration of the acid, and k_2 is the second-order rate constant of the reaction. The logarithm of the second-order rate constant is linearly related to the aqueous pK_a of the catalyst. The experimental results suggest that the bonds at the end of the polymer chain may be slightly more reactive than the internal linkages, but overall, the reaction proceeds to a large extent *via* random scission. Strain at the *ortho*-ester linkages may play a role in the determination of its reactivity.

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Synthesis and *In Vitro* Antiviral Activity of 3′-*O*-Acyl Derivatives of 5′-Amino-5′-deoxythymidine: Potential Prodrugs for Topical Application

TAI-SHUN LIN

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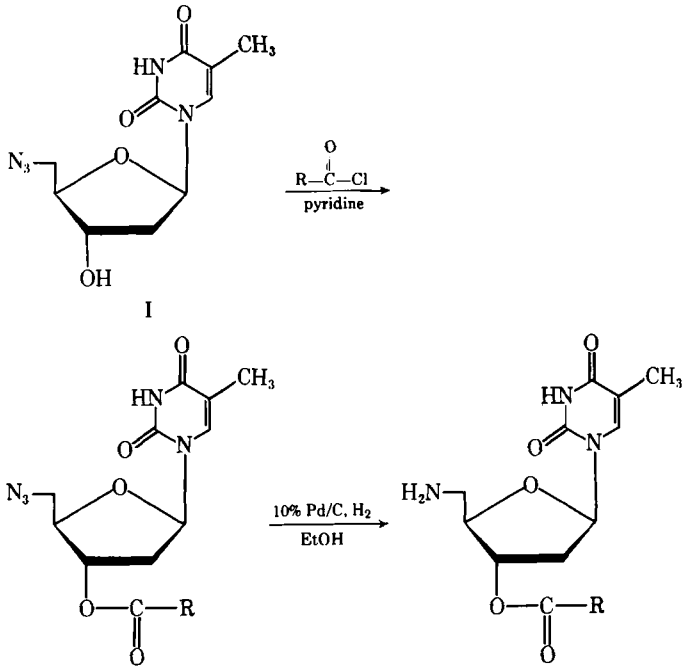
Abstract □ A series of 3′-*O*-acyl derivatives of 5′-amino-5′-deoxythymidine (5′-NH_2-TdR) (IIIa–j) was synthesized by acylation of 5′-azido-5′-deoxythymidine (I). The resulting acetoxy azides were reduced by catalytic hydrogenation to give the corresponding amines. The antiviral activity against herpes simplex virus type 1 (HSV-1) *in vitro*, the aqueous solubilities, and the octanol–water partition coefficients of these compounds were determined. All these derivatives have shown potency against HSV-1 virus similar to the parent compound, except the aromatic and highly branched aliphatic esters, IIIi and IIIj, which are less active. Because of their markedly improved lipophilicity, these compounds are believed to penetrate the biological membranes more easily, and thus, would be more effective for the topical treatment of cutaneous herpes virus infections.

Keyphrases □ 3′-*O*-Acyl derivatives of 5′-amino-5′-deoxythymidine—synthesis, antiviral activity □ Prodrugs—potential, topical application. 3′-*O*-acyl derivatives of 5′-amino-5′-deoxythymidine

The 5′-amino analogue of thymidine (5′-NH_2-TdR) has demonstrated potent antiviral activity against herpes simplex virus type 1 (HSV-1) in the complete absence of toxicity to the uninfected host Vero cells in culture (1, 2). This compound was therapeutically effective in the topical therapy of herpetic keratouveitis in rabbits, and systemic administration into the neonatal mouse revealed no adverse effect *in vivo* or by the histopathological examination (3). Chen *et al.* (4) have recently found that 5-NH_2-TdR was a substrate for the HSV-1-encoded thymidine kinase but was not a substrate for the cellular thymidine kinase. The complete lack of toxicity of 5′-NH_2-TdR to the uninfected Vero cells is probably due to the lack of the herpes simplex virus-induced thymidine kinase which is required for activation (4, 5).

Recently, Baker *et al.* (6) have reported the synthesis of a series of 5′-*O*-acyl derivatives of 9-β-D-arabinofuranosyladenine (vidarabine, ara-A). These compounds were designed as prodrugs for vidarabine and have demonstrated better lipophilicity, and thus, the potential for improved membrane transport over vidarabine. Among these compounds, the 5′-*O*-valeryl derivative has shown a marked increase in both lipophilicity and antiviral activity compared with that of vidarabine.

Recently, Hettinger *et al.* (7) have reported that both 5-iodo-2′-deoxyuridine (idoxuridine, IUdR) and 5-iodo-3′,5′-di-*O*-acetyl-2′-deoxyuridine (Ac_2IDU), an *O*-acetyl derivative of IUdR, were effective against keratitis. However, Ac_2IDU was significantly more effective than the placebo 1 d sooner than was idoxuridine. The greater lipid solubility of the Ac_2IDU that resulted in greater epithelial penetration could account for this difference. Based on these findings, a series of 3′-*O*-acyl derivatives of 5′-NH_2-TdR has been synthesized. Preliminary studies indicated that all these compounds retain the same degree of antiviral activity in comparison with the parent compound, except the 3′-*O*-*tert*-butylacetyl and 3′-*O*-benzoyl esters, IIIi and IIIj, which were found to be less active. The lipophilicities of these derivatives increased



Scheme I

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