# Calculation of Hydrolytic Rate Constants of Poly(ortho ester)s from Molecular Weights Determined by Gel Permeation Chromatography

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***Purpose.*** To obtained rate constants from weight-averaged ($M_w$) or z-averaged ($M_z$) molecular weights for polymers of Schule-Flory distribution and undergoing random scission. These constants were compared with those obtained by parallel $^1$HNMR studies.

***Methods.*** The hydrolysis of two poly(ortho ester)s were followed by $^1$HNMR and gel permeation chromatography (GPC).

***Results.*** Equations to convert number-averaged ($M_n$), $M_w$ and $M_z$ into fraction of backbone remaining ($f_c$) were derived. First-order hydrolytic rate constants of two poly(ortho ester)s; DETOSU-HD and DETOSU-CDM were calculated using these relationships. The rate constants calculated from $^1$HNMR, $M_z$ and $M_w$ were 0.215, 0.218 and 0.182 $hr^{-1}$, respectively, for DETOSU-CDM and 0.152, 0.086 and 0.038 $hr^{-1}$ for DETOSU-HD. The large discrepancy in the rates determined by $^1$HNMR and GPC in the latter case was attributed to that the detector response (refractive index) of the monomers was lower than that of the high molecular weight polymer. The difference is small in the case of DETOSU-CDM, and the rates calculated from GPC data were comparable or nearly identical to that obtained from $^1$HNMR data.

***Conclusions.*** Although GPC can yield rapid and valuable kinetic data for the degradation of biodegradable polymers, the system, however, must be carefully calibrated to account for the variations in Mark-Houwink coefficients and in the response of the mass detector between the high and low MW polymers.

KEY WORDS: biodegradable polymers; gel permeation chromatography; hydrolysis; poly(ortho ester)s; rate constant.

## INTRODUCTION

Biodegradable poly(ortho ester)s have been effective platforms for long-term drug delivery (1). Drug release from these polymers is controlled by erosion and/or diffusion (1), with both of these mechanisms dependent on degradation of the polymer. Conventionally, degradation is monitored by the loss of molecular weight (MW). The method of choice for MW determination is gel permeation chromatography (GPC). Number-averaged ($M_n$), weight-averaged ($M_w$), z-averaged ($M_z$) and viscosity-averaged ($M_v$) molecular weights can be calculated from the MW distribution. However, reports in the literature vary in the MW average selected for degradation rate calculations. For example, Pitt et al. (2) used $M_n$ for the hydrolysis of poly(ϵ-caprolactone) and Kenley et al. (3) used $M_w$ for the hydrolysis of poly(D,L-lactide-co-glycolide). Peak molecular weights also have been used (4) to describe the kinetic degradation process. In all cases these molecular weights were obtained either by direct calibration against polystyrene standards (5) or by the "universal calibration method" (6). The latter method is more reliable but requires Mark-Houwink (M-H) coefficients for the specific polymer. Since the polymer of interest is usually polydispersed, Hamielec (7) demonstrated that $M_n$ should be chosen for calculation of M-H coefficients. Again, literature reports have not been consistent in selecting M-H coefficients for the universal calibration. For example, Pitt et al. (2) used M-H coefficients calculated from $M_n$'s, van Dyck et al. (8) and Kenley et al. (3) used M-H coefficient calculated from $M_v$'s (iterated from GPC traces) and Pryde et al. (9) used M-H coefficients from $M_w$'s. The purposes of the present manuscript were to contrast the different approaches and propose methods to calculate rate constants from GPC data. Hydrolyses of two poly(ortho ester)s were investigated as examples. The rates calculated from GPC data were compared to rates calculated from parallel $^1$HNMR studies.

## MATERIALS AND METHODS

*Trans*-cyclohexane-1,4-dimethanol (CDM) was obtained from Eastman Chemical Company. Tetrahydrofuran (THF; nonspectral grade) was purchased from Baxter (Muskegon, MI). Monomeric diketene acetal (3,9-bis(ethylidene)-2,4,8,10-tetraoxaspiro[5,5]undecane; DETOSU) was synthesized by Merck Research Laboratories (Rahway, NJ) using the method reported by Heller et al. (10) p-Dioxane (SureSeal™), hexane-1,6-diol (HD), dichloroacetic acid, deuterium oxide (99.5% D), triethyamine and p-dioxane-$d_8$ were obtained from Aldrich Chemical Company (Milwaukee, WI). Polystyrene standards were obtained from Polymer Laboratories. HD was distilled under reduced pressure before use. The remaining chemicals were used as received.

### Synthesis of the Poly(ortho Ester)s

HD (11.82 g) was placed into an oven-dried round bottom flask (250 ml) and dissolved in 100 ml of p-dioxane. The flask was equipped with a reflux condenser and the head space was purged by dry nitrogen. DETOSU (21.22 g) was added via a dry syringe and the reaction mixture was refluxed for 16 hours. One-ml of triethylamine was added to the polymer solution before decanting into a Teflon™ dish. The solvent and triethylamine were evaporated in vacuo (100°C, 5 μ Hg; 3 days). The resulting slab was cut into small pieces and stored desiccated in a freezer (−4°C). DETOSU-CDM was prepared similarly, using CDM in place of HD. The $M_n$ of DETOSU-CDM and DETOSU-HD determined by membrane osmometry (Polymer Science Laboratories) were 23,500 and 25,500, respectively.

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### Hydrolytic Studies

Polymer samples (40 mg) were placed into a 2 ml volumetric flask and dissolved in ca. 1.8 ml of p-dioxane-$d_8$. The solution temperature was equilibrated at 37°C for ca. 30 minutes before the addition of 75 μl of $D_2O$ and 0.2 ml dichloroacetic acid (20.1 mM in p-dioxane-$d_8$). The volume was brought to 2 ml with p-dioxane-$d_8$ and the solution was filtered (0.45 μ nylon filter) into a screw-capped NMR tube and immersed in a 37°C water bath. Aliquots (80 μl) of the solution were collected every 5–10 minutes during the first hour. The acid catalyzed hydrolysis was instantaneously stopped by addition of 0.7 ml of triethylamine solution (0.05% in THF). These samples were analyzed by GPC. The hydrolysis in the remaining solution was monitored periodically by $^1$HNMR (Brucker, ACE-200). The GPC was composed of a solvent delivery pump (ISCO), a pressure dampener (ISCO), an autosampler (Micromeretics; 150 μl sample loop), a guard column (Polymer Laboratories, 10 μ, 50 mm × 7.0 mm) and a column set consisting of one $10^3$ Å and three 50 Å columns (Polymer Laboratories, 10 μ, 300 mm × 7.5 mm) connected in series. The temperature of the columns was maintained at 30°C by thermal jackets. Nonspectral grade THF (filtered) was the mobile phase at a flow rate of 1.0 ml/minute. Effluent from the columns was divided equally between a refractive index (RI) detector (Shimadzu, 6A) and a differential viscosity detector (Viscotek, Model 5000). Chromatograms were generated by an A/D converter using Viscotek software.

### Determination of dn/dc

Polymer and monomer samples (n = 4) were weighed then dissolved in 5 ml of THF. The dn/dc values (increment of refractive index with respect to changing concentration) were calculated from the GPC chromatograms using the following equation:

$$\frac{dn}{dc} = \frac{(A_s/w_s) \cdot 0.195}{(A_{ps}/w_{ps})}$$

where $A_s$, $w_s$ and $A_{ps}$, $w_{ps}$ are the peak areas and weights of the sample and the polystyrene standard, respectively. The dn/dc value of polystyrene (THF; 30°C) was 0.195 $cm^3/g$ (11).

## RESULTS AND DISCUSSION

### Calculation of Rate Constants from $M_n$

The poly(ortho ester)s were comprised of a single type of labile bond (C) and previously were shown to degrade by a random scission mechanism (12). The classical statistical treatment for polymers undergoing random scission was first reported by Kuhn (13) and later reviewed by Jellinek (14) and by Grancher (15). $M_n$ can be related to the concentration of end-groups as follows.

Assuming the molecular weight of the repeating unit (m) is constant (contribution of the end units is negligible), the concentration of the hydrolytic product (E; monomer and polymer end-groups) can be related to $M_n$ by Eq. 1,

$$[E] = w/(M_n \cdot V) = w/(m \cdot V) \cdot (1/DP_n) \quad (1)$$

where w is the polymer sample weight, V is the volume and $DP_n$ is the number-averaged degree of polymerization ($M_n$/m). In the neat state, w/(m · V) is equivalent to $1/V_m$ where $V_m$ is the molar volume of the repeating unit of the polymer. The concentration of the total repeating units (mass balance) in the reaction mixture is:

$$[C] + [E] = [C]_o + [E]_o = w/(m \cdot V) \quad (2)$$

where $[C]_o$ and $[E]_o$ are the corresponding concentrations of [C] and [E] at t = 0. Thus, the mole fraction of E, $f_E$, with respect to the total units, $[C]_o + [E]_o$, is,

$$f_E = [E]/([C]_o + [E]_o) = 1/DP_n \quad (3)$$

Assuming x is the number of scissions per molecule for a polymer with $DP_n^\circ - 1$ linkages in the backbone (i.e., an initial number-averaged degree of polymerization of $DP_n^\circ$), the degree of degradation, α, is defined as (14)

$$\alpha \equiv x/(DP_n^\circ - 1) \quad (4)$$

If the initial molecular weight is high, i.e. $[E]_o \approx 0$, and $f_E$ approximates the degree of degradation:

$$\alpha = ([E] - [E]_o)/[C]_o \approx [E]/([C]_o + [E]_o) = f_E \quad (5)$$

From Eq. 1 and 2, the concentration of intact polymer backbone bonds can be expressed as

$$[C] = w/(m \cdot V) \cdot (1 - 1/DP_n) \quad (6)$$

Similarly, the mole fraction of intact backbone bonds, $f_C$, can be expressed as

$$f_C = [C]/([C]_o + [E]_o) = 1 - 1/DP_n \approx 1 - \alpha \quad (7)$$

These expressions are independent of the initial molecular weight distribution, mode of scission, mechanism and the kinetic order of degradation. Kinetics can be described using [C] or [E] ($f_C$ or $f_E$) through measuring $M_n$ ($DP_n$) by GPC, osmometry, etc. For example, a first-order loss of the backbone bonds can be expressed as

$$\ln [C] = \ln [C]_o - k_1 \cdot t \quad (8)$$

where $k_1$ is the first-order hydrolytic rate constant. Substituting Eq. 6 into Eq. 8 gives

$$\ln(1 - 1/DP_n) = \ln(1 - 1/DP_n^\circ) - k_1 \cdot t \quad (9)$$

Equation 9 is identical to that reported by Wolfram (16) using formulas developed by Kuhn (13). When the $DP_n$'s are large, Eq. 9 reduces to Eq. 10 (14).

$$1/DP_n = 1/DP_n^\circ + k_1 \cdot t \quad (10)$$

These equations can be expressed in terms of the number of cleavages per molecule (x) if $DP_n^\circ$ is known. Since

$$DP_n \equiv DP_n^\circ/(1 + x) \quad (11)$$

Eq. 9 becomes

$$\ln[1 - (1 + x)/DP_n^\circ] = \ln[1 - 1/DP_n^\circ] - k_1 \cdot t \quad (12)$$

Equation 12 can be expanded as a Taylor series when x is small (terms with order >1 were dropped), and $k_1$ can be calculated from Eq. 13:

$$x = k_1 \cdot (DP_n^\circ - 1) \cdot t \quad (13)$$

Thus, x is directly proportional to the reaction time if the degradation is first-order. Assuming the hydrolysis follows an autocatalytic mechanism, then

$$-d[C]/dt = k_2 \cdot [C] \cdot [E] = k_2 \cdot [C] \cdot ([C]_o + [E]_o - [C]) \quad (14)$$

where $k_2$ is the catalytic constant. The integrated form of Eq. 14 can be rearranged into

$$\ln\left(\frac{1}{[C]} - \frac{1}{[C]_o + [E]_o}\right) = \ln\left(\frac{1}{[C]_o} - \frac{1}{[C]_o + [E]_o}\right) + k_2 \cdot ([C]_o + [E]_o)\, t \quad (15)$$

Substituting Eq. 2 and 6 into Eq. 15, one obtains

$$\ln(DP_n - 1) = \ln(DP_n^\circ - 1) - k_2 \cdot w/(m \cdot V) \cdot t \quad (16)$$

If $DP_n \gg 1$, Eq. 16 becomes

$$\ln(DP_n) = \ln(DP_n^\circ) - k_2 \cdot w/(m \cdot V) \cdot t \quad (17)$$

Equation 17 has been reported by Pitt (2). Equation 17 can also be expressed in terms of x, viz.,

$$\ln(x + 1) = k_2 \cdot w/(m \cdot V) \cdot t \quad (18)$$

In contrast to the proposal of Kenley et al. (3), a first-order dependence of x (or more precisely, x + 1) on the reaction time is consistent with an autocatalytic mechanism.

### The Relationship Between $M_w$ and $M_z$ and the Backbone Bonds

As shown in the above derivation, rate constants are readily calculated from the loss of $M_n$. Unfortunately, GPC $M_n$'s are sensitive to the integration limits (17). Hence, rate calculated from GPC $M_n$ data are prone to errors. GPC $M_w$ and $M_z$ data are less sensitive to the integration limits than $M_n$ (Fig. 4), and theoretically, accurate rate constants can be reduced from these MW's. Relationships between $DP_w$ and the degree of degradation for initially Schule-Flory distributed polymers undergoing random scission have been reported by Montroll and Simha (18) and by Sakurada and Okamura (19). However, selection of the applicable equation is dependent on the initial degree of polymerization and the extent of degradation. A method to obtain x from $DP_w$ and $DP_z$ for polymers of a known initial distribution has been reported by Inokuti (20). Specific equations for polymers with initial Poisson distribution were also given (20). These equations, however, are probably most applicable when the degree of degradation is small, since the polydispersity calculated by these equations does not converge to 1 when x approaches complete degradation ($DP_n^\circ - 1$). Poly(ortho ester)s are step-growth condensation copolymers which follow Schule-Flory MW distribution or the "most probable distribution" (21). Equations to convert $M_w$ and $M_z$ to $f_C$ or x for this type of polymers can be derived as follows:

Grancher (15) reported the weight fraction of an i-mer ($w_i$) in the distribution, at a given $\alpha$ and $DP_n^\circ$, is

$$w_i = i \cdot [1 - (1 - \alpha) \cdot (1 - 1/DP_n^\circ)]^2 \cdot [(1 - \alpha) \cdot (1 - 1/DP_n^\circ)]^{i-1} \quad (19)$$

The definition of weight-averaged degree of polymerization ($DP_w$) is

$$DP_w = \frac{\sum_{i=1}^{n}(i \cdot w_i)}{\sum_{i=1}^{n} w_i} \quad (20)$$

Assuming

$$y = (1 - \alpha) \cdot (1 - 1/DP_n^o) \quad (21)$$

Substituting Eq. 19 and 21 into Eq. 20, one obtains

$$DP_w = \frac{\sum_{i=1}^{n} i^2 \cdot (1 - y)^2 \cdot y^{i-1}}{\sum_{i=1}^{n} i \cdot (1 - y)^2 \cdot y^{i-1}} = \frac{(1 + 4y + 9y^2 + 16y^3 + 25y^4 + \cdots)}{(1 + 2y + 3y^2 + 4y^3 + 5y^4 + \cdots)} = 1 + 2 \cdot (y + y^2 + y^3 + y^4 + \cdots) \quad (22)$$

Since $1 + y + y^2 + y^3 + y^4 + \cdots = 1/(1 - y)$ if $y < 1$, Eq. 22 becomes

$$DP_w = \frac{1 + y}{1 - y} \quad (23)$$

Substituting Eq. 7 and 21 into Eq. 23, one obtains

$$DP_w = \frac{1 + f_c \cdot (1 - 1/DP_n^o)}{1 - f_c \cdot (1 - 1/DP_n^o)} \quad (24)$$

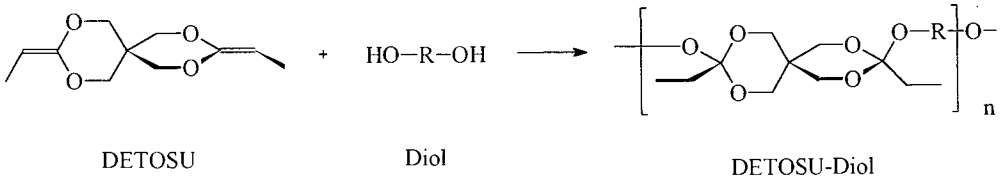
Thus, $f_c$ can be calculated if $DP_w$ and $DP_n^o$ are known. Similarly,

$$DP_z = \frac{\sum_{i=1}^{n} i^2 \cdot w_i}{\sum_{i=1}^{n} i \cdot w_i} \quad (25)$$

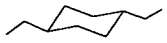
Substituting Eq. 19 and 21 into Eq. 25, one has

$$DP_z = \frac{\sum_{i=1}^{n} i^3 \cdot (1 - y)^2 \cdot y^{i-1}}{\sum_{i=1}^{n} i^2 \cdot (1 - y)^2 \cdot y^{i-1}} = 1 + 4y + 2y^2 + 4y^3 + 2y^4 + 4y^5 + 2y^6 + \cdots$$

Synthesis:

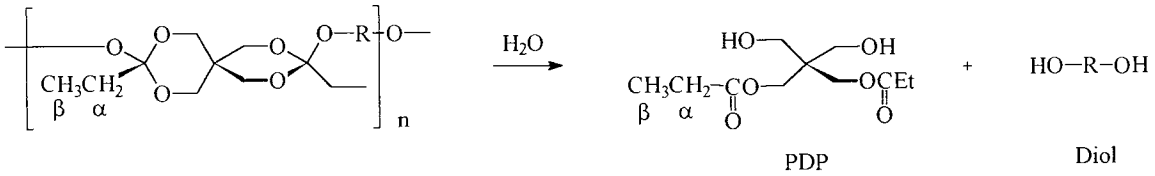



R= -$(CH_2)_6$- HD



*t*-CDM

Hydrolysis:




**Scheme 1.**

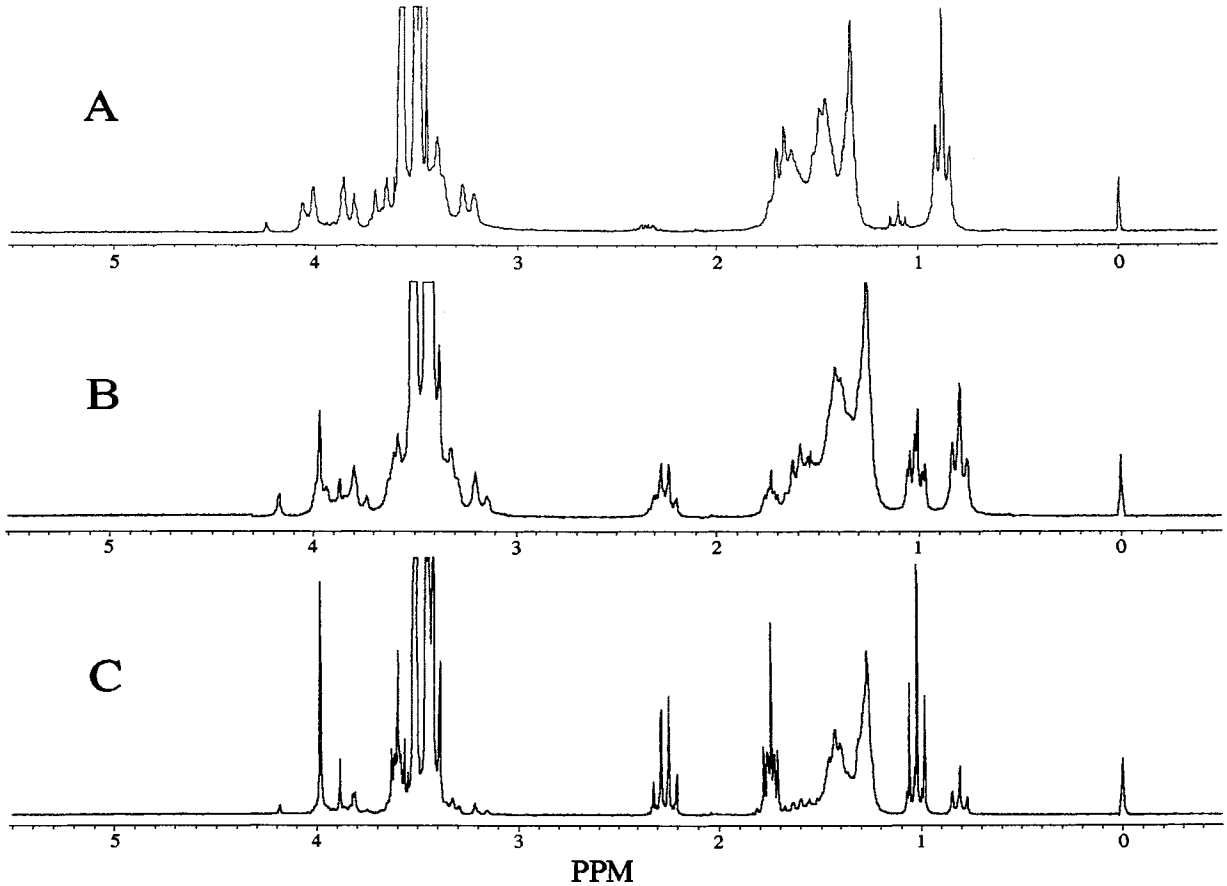



Fig. 1. $^1$HNMR spectra of DETOSU-HD in p-dioxane-$d_8$ containing 2.01 M of $D_2O$ and 2 mM dichloroacetic acid (37°C). Spectra taken when 95% (A), 59% (B) and 18% (C) of the ortho ester bonds remained.

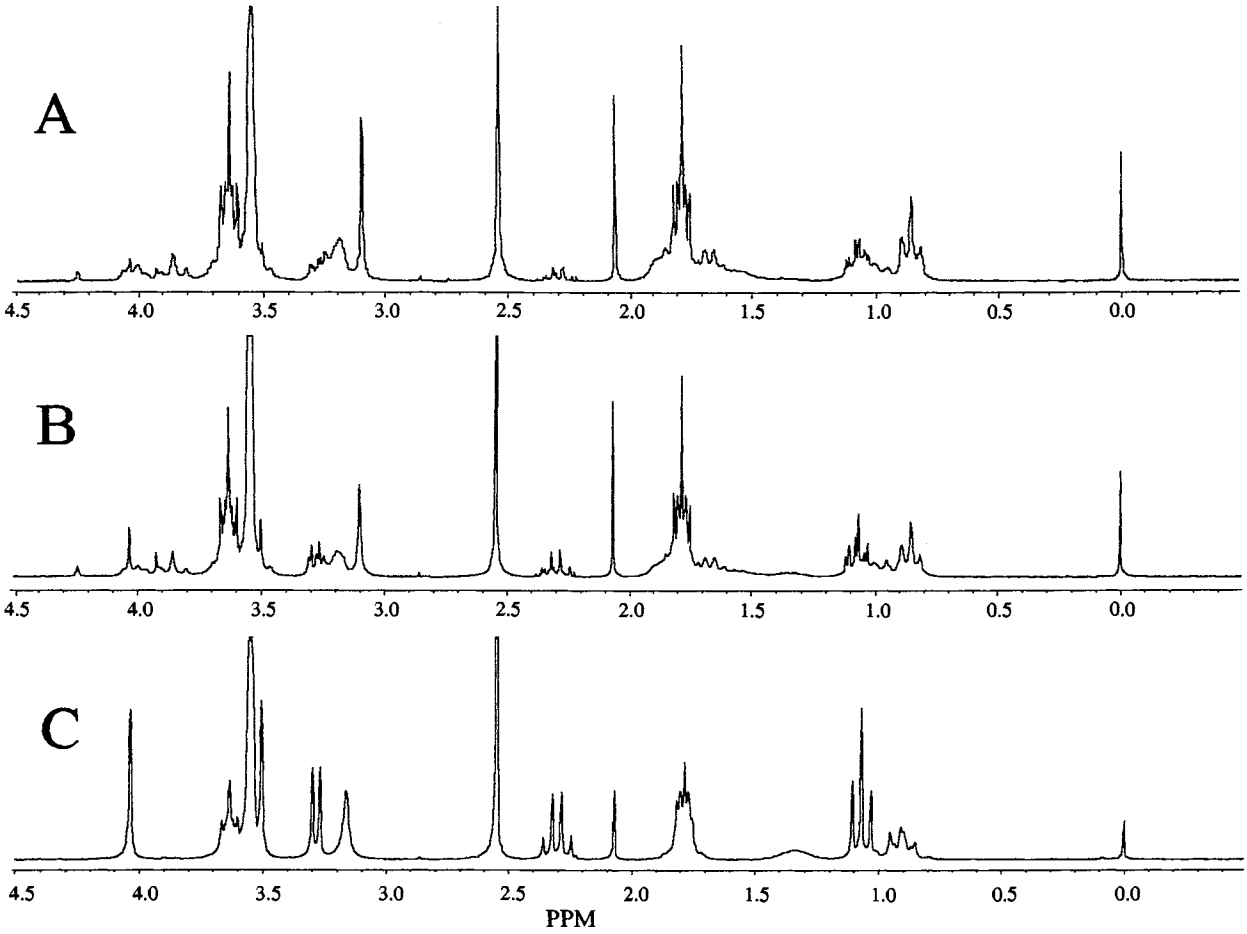



Fig. 2. $^1$HNMR spectra of DETOSU-CDM taken when 26% (A), 33% (B), and 74% (C) of the backbone ortho ester bonds were hydrolyzed at 37°C in p-dioxane-$d_8$ containing $D_2O$ (2.01 M). Hydrolysis was catalyzed by 2.0 mM of dichloroacetic acid.

$$= 1 + 2y \cdot (1 + y + y^2 + y^3 + \cdots) + 2y \cdot (1 + y^2 + y^4 + y^6 + \cdots)$$

$$= 1 + \frac{2 \cdot y}{1 - y} + \frac{2 \cdot y}{1 - y^2} = \frac{1 + 4 \cdot y + y^2}{1 - y^2} \quad (26)$$

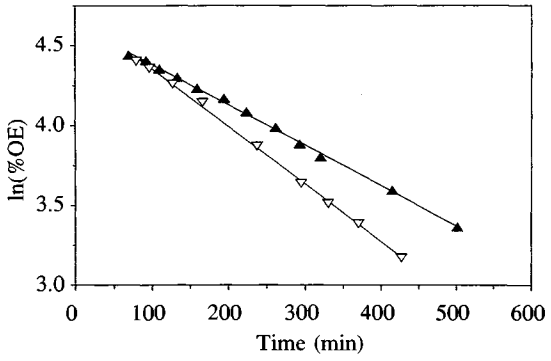
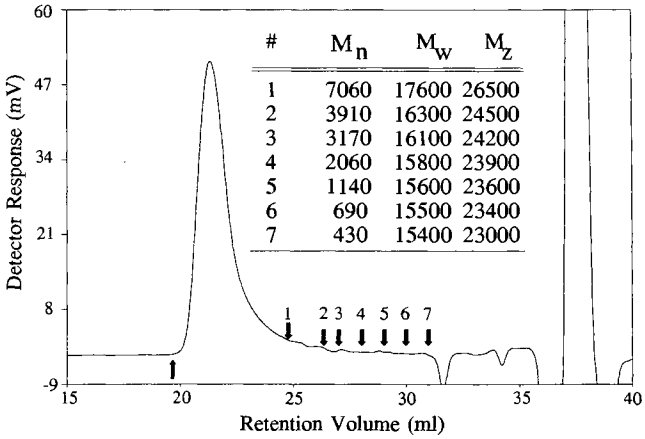



Fig. 3. Hydrolysis of DETOSU-CDM (▽) and DETOSU-HD (▲) in p-dioxane-$d_8$ containing $D_2O$ (2.01 M) at 37°C, reaction catalyzed by 2.0 mM of dichloroacetic acid). Data obtained by $^1$HNMR.

$$DP_z = \frac{1 + 4 \cdot f_c \cdot (1 - DP_n^o) + f_c^2 \cdot (1 - 1/DP_n^o)^2}{1 - f_c^2 \cdot (1 - DP_n^o)^2} \quad (27)$$

Substituting Eq. 4 and 21 into Eq. 23 and 26, x can be calculated from the GPC $DP_w$ and $DP_z$ using Eq. 28 and 29.




| # | $M_n$ | $M_w$ | $M_z$ |
|---|---|---|---|
| 1 | 7060 | 17600 | 26500 |
| 2 | 3910 | 16300 | 24500 |
| 3 | 3170 | 16100 | 24200 |
| 4 | 2060 | 15800 | 23900 |
| 5 | 1140 | 15600 | 23600 |
| 6 | 690 | 15500 | 23400 |
| 7 | 430 | 15400 | 23000 |

Fig. 4. A sample gel permeation chromatogram of DETOSU-CDM. The molecular weights were calculated using integration limits indicated.

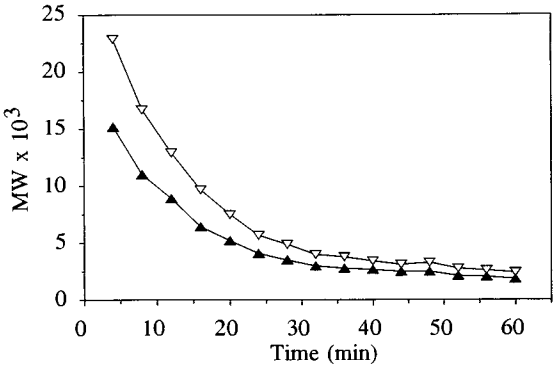



Fig. 5. Weight-averaged (▲) and z-averaged (▽) MW determined by GPC for the hydrolysis of DETOSU-CDM in p-dioxane-$d_8$ containing 2.01 M $D_2O$ at 37°C. Hydrolysis was catalyzed by 2.0 mM of dichloroacetic acid.

$$DP_w = 2DP_n°/(1 + x) - 1 \quad (28)$$

$$DP_z = 3DP_n°/(1 + x) - DP_n°/(2DP_n° - 1 - x) - 1 \quad (29)$$

### Hydrolyses of DETOSU-CDM and DETOSU-HD

*1. HNMR Spectra.* Poly(ortho ester)s were prepared from condensation of DETOSU and a diol (*trans*-cyclohexane-1,4-dimethanol (CDM) or hexane-1,6-diol (HD) (Scheme 1)) (10). Upon exposure to aqueous environments, these polymers are hydrolyzed into pentaerythritol dipropionate and the parent diol (Scheme 1) (22). The $^1$HNMR spectra taken during the hydrolysis of DETOSU-HD are shown in Fig. 1. The peaks corresponding to the protons of the α-methylene and the β-methyl of the orthopropionate were at δ1.6 (not resolved) and δ0.88 ($Me_1$; triplet), respectively. The triplets at δ1.05 ($Me_2$) and quartets at δ2.27 were assigned, respectively, to the α-methylene and β-methyl protons of the propionate reaction products. During hydrolysis, the peak areas corresponding to the orthopropionate continuously decreased while those of the propionate reaction products increased. The percentages of ortho ester remaining (%OE) of DETOSU-HD were calculated from the areas corresponding to the methyl protons using Eq. 30.

$$\%OE = Me_1/(Me_1 + Me_2) \cdot 100\% \quad (30)$$

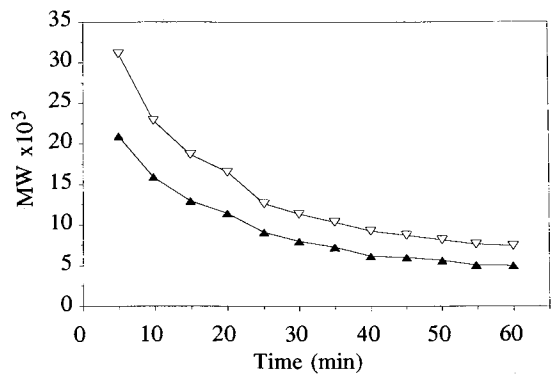



Fig. 6. Weight-averaged (▽) and z-averaged (▲) MW determined by GPC for the hydrolysis of DETOSU-HD in p-dioxane-$d_8$ containing 2.01 M $D_2O$ at 37°C. Hydrolysis was catalyzed by 2.0 mM of dichloroacetic acid.

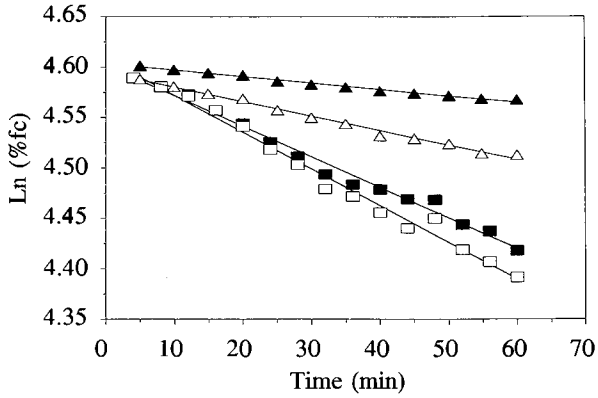



Fig. 7. Hydrolysis of poly(ortho ester)s in p-dioxane-$d_8$ containing $D_2O$ (2.01 M) and catalyzed by 2.0 mM of dichloroacetic acid at 37°C. Fraction of backbone remaining ($f_c$) calculated from GPC $DP_w$'s (■) and $DP_z$'s (□) for DETOSU-CDM and GPC $DP_w$'s (▲) and $DP_z$'s (△) for DETOSU-HD.

For DETOSU-CDM, these protons were not resolved (Fig. 2). Therefore, a small amount of acetophenone was introduced as an internal standard. The %OE's were calculated from the area ratio of the α-methylene protons (A; δ2.27) of the propionate degradation products and the methyl protons of acetophenone ($A_{ac}$; δ2.55, singlet) using Eq. 31.

$$\%OE = [(A_\infty/A_{ac} - A/A_{ac})/(A_\infty/A_{ac})] \cdot 100\% \quad (31)$$

where $A_\infty$ is the area of A at $t = \infty$. The degradation profiles of DETOSU-HD and DETOSU-CDM are shown in Fig. 3. The hydrolysis of the backbone bonds appeared to be first-order and the rate constants were 0.215 and 0.152 $hr^{-1}$ for DETOSU-CDM and DETOSU-HD, respectively.

*2. GPC Studies.* Figure 4 shows a GPC chromatogram of DETOSU-CDM. The molecular weight-averages can be calculated for any given pair of integration limits. The limit at the onset of the peak ($V_{R1}$; high molecular weight) can routinely be set without difficulty (at 19.77 ml). Setting the integration limit at the side of the high retention volume ($V_{R2}$; low MW), however, is somewhat subjective. The calculated MW averages are dependent on these limits. As shown in Fig. 4, $M_n$ was reduced by 93.9% while $M_w$ and $M_z$ were reduced by 12.5% when the $V_{R2}$ was extended from 24.68 to 31.0 ml. In the present studies, the $V_{R2}$ was set at 31.0 ml as studies showed that all monomers had been eluted by this time. The MW vs. time profiles of DETOSU-CDM and

Table I. The dn/dc values of DETOSU-CDM, DETOSU-HD and pentaerythritol dipropionate (PDP), t-cyclohexane-1,4-dimethanol (CDM), hexane-1,6-diol (HD) and polystyrene

| Substrate | dn/dc ($cm^3/g$) |
|---|---|
| DETOSU-CDM | 0.0684 ± 0.00162 |
| DETOSU-HD | 0.0732 ± 0.00130 |
| PDP | 0.0527 ± 0.00057 |
| CDM | 0.1008 ± 0.00105 |
| HD | 0.0398 ± 0.00032 |
| PDP/CDM (1:1) | 0.0704[a] |
| PDP/HD (1:1) | 0.0489[a] |

[a] Calculated from the molar mixtures (1:1) of the components.

DETOSU-HD are presented in Fig. 5 and 6, respectively. The rate constants calculated from $M_w$ and $M_z$ (using Eq. 24 or 27 and Eq. 8) for DETOSU-CDM (Fig. 7) were 0.182 and 0.218 $hr^{-1}$, respectively, and 0.038 and 0.086 $hr^{-1}$ for DETOSU-HD (Fig. 7). It is noted that the GPC rates calculated for DETOSU-CDM were similar to those obtained from the $^1$HNMR studies while those calculated for DETOSU-HD were significantly smaller than those obtained by $^1$HNMR. $^1$HNMR monitored more than 95% of the degradation, rates calculated by this method should be more reliable than those obtained by the GPC method. The latter method measured a small percentage of the entire degradation process. It is noted that the rate calculated from the $M_z$'s in the DETOSU-HD case was at least two-fold than those from the $M_w$'s. This problem could be associated with extending the GPC integration limit to include the low molecular weight polymers. It has been reported that the Mark-Houwink relationship of polystyrene is nonlinear in the low MW (<10,000) range (23). However, this problem was not likely to occur as the differential viscosity detector directly measured the intrinsic viscosity of each slice of the chromatogram without using the M-H equation to calculate the hydrodynamic volume. Therefor the problem more likely resulted from the refractive index detector (RI; a mass detector). The GPC software assumes that the dn/dc value is a constant over the entire MW range. However, it has been reported that the dn/dc value of polystyrene was constant only if the MW was larger than 10,000, and continuously decreasing as the MW become lower (24). The dn/dc values of POE's can also be dependent on the MW. Table I lists the dn/dc values of the polymers studied and their decomposition products. The dn/dc values of degrading polymers are likely to change from the those of the high MW polymer to that of the degradation products (1:1 molar mixture of PDP and the diol) as the hydrolysis proceeds. The extent of change for the hydrolysis of DETOSU-HD (from 0.0732 to 0.0489) was quite large. Therefore, the mass of the low MW fraction of DETOSU-HD would have been underestimated and the MW's overestimated. Consequently, the degree of degradation and the rate constants could have been underestimated. Such bias is expected to be greater for $M_w$ than for $M_z$ because $M_z$ is the ratio of the third moment over the second moment of the distribution while the $M_w$ is the ratio of the second moment over the first moment of the distribution (25); thus the low MW polymers are weighted more heavily in the calculation of $M_w$ than $M_z$. The change in dn/dc values was small (from 0.0684 to 0.0704) for the hydrolysis of DETOSU-CDM, and the discrepancy in $^1$HNMR and GPC rates would consequently be minimal.

## CONCLUSIONS

In spite of the inconsistencies encountered in this first attempt, it has been shown that gel permeation chromatography can yield rapid and valuable kinetic data for the degradation of biodegradable polymers. However, the GPC system must be carefully calibrated (or corrected) to account for the variations in Mark-Houwink coefficients and in the response of the mass detector between the high and low MW polymers.

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