Macromolecules **1989,** *22,* 2117–2122 **2117**

Solid-State and Solution Stability of Poly(anhydrides) and Poly(esters)

Abraham J. Domb[†] **and Robert Langer***

Massachusetts Institute of Technology, Department of Chemical Engineering, Cambridge, Massachusetts 02139. *Received November 20, 1987*

ABSTRACT: The stability of poly(anhydrides) composed of the diacids sebacic acid (SA), suberic acid (SuA), adipic acid (AA), bis(*p*-carboxyphenoxy)methane (CPM), 1,3-bis(*p*-carboxyphenoxy)propane (CPP), 1,6-bis(*p*-carboxyphenoxy)hexane (CPH), and phenylenedipropionic acid (PDP) in solid state and in organic solutions is reported. Aromatic poly(anhydrides) (poly(CPH) and poly(CPM)) maintained their original molecular weight in both solid state and solution while aliphatic poly(anhydrides) (poly(SA) and poly(PDP)) decreased in molecular weight over time. The decrease in molecular weight shows first-order kinetics with activation energies of 7.5 kcal·mol^{-1}·K^{-1}. The decrease in molecular weight was explained by an internal anhydride interchange mechanism as revealed from elemental and spectral analysis (IR and ^{13}C and ^{1}H NMR). The depolymerization in solution can be catalyzed by metals. Among several metals tested, copper and zinc were the most effective. Studies on the stability of aliphatic poly(esters) in chloroform showed that poly(orthoesters) depolymerized over time while poly(α-esters) and poly(ethylenesuccinate) remained intact. The solid-state and organic solution stability of the polymers do not correlate with their hydrolytic stability.

Introduction

The stability of polymers under various conditions (e.g., oxidation, hydrolysis, heat) and the properties of polymers in solution are well documented.[1,2] However, very little is known about the stability of polymers in solid state or in solution under inert conditions. We report the results of studies on the stability of poly(anhydrides) in solid state and in organic solution under anhydrous conditions. While the hydrolytic instability and thermal decomposition behavior of these polymers have been described,[3-8] these are the first studies to investigate the long-term solid-state and solution stability of poly(anhydride) and to examine the effect of polymer composition on poly(anhydride) destabilization.

Poly(anhydrides) composed of the monomers sebacic acid (SA), suberic acid (SuA), adipic acid (AA), bis(*p*-carboxyphenoxy)methane (CPM), 1,3-bis(*p*-carboxyphenoxy)propane (CPP), 1,6-bis(*p*-carboxyphenoxy)hexane (CPH), and phenylenedipropionic acid (PDP) were used in this study. All polymers used were soluble in organic solvents—a requirement for analytical purposes. Since there is a similarity between the thermal stability of poly(anhydrides) and poly(esters),[9] we subsequently studied the stability in solution of several poly(esters), including poly(orthoesters) and poly(lactic acid). The stability properties of all of these polymers are important since they have been considered for use as erodible materials in medicine.[5-7,10-12]

Results and Discussion

Solid-State Stability of Poly(anhydrides). Poly(anhydrides) were stored anhydrous under vacuum or under dry argon, and the molecular weight was determined over time by intrinsic viscosity and gel permeation chromatography (GPC). Identical results were obtained under both storage conditions. Figure 1 demonstrates the change in molecular weight over time when polymer was stored at 21 °C. Aromatic poly(anhydrides) (poly(CPM) and poly(CPH)) maintained their original molecular weight over the entire period studied (12 months). However, aliphatic poly(anhydrides), poly(SA) and poly(PDP) with initial weight average molecular weights (M_w) of 137 500 and 43 000, respectively, depolymerized to reach steady-state M_w levels of 78 800 and 23 000. Copolymers of CPP (aromatic) and SA (aliphatic) depolymerized according to their aromatic content (Figure 1). Increasing the temperature enhanced depolymerization. Thus, poly(SA) of M_w = 137 800 stored at 37, 21, 0, and −10 °C had after 60 days weight average M_w of 65 800, 78 000, 96 600, and 118 400, respectively. GPC analysis performed during the storage process revealed that the depolymerization phenomenon primarily affected the high molecular weight fractions of polymers (Figure 2). As a result, the number average molecular weight (M_n) was effected to a lesser extent than M_w.

Table I
Depolymerization Rates of Poly(anhydrides) and Poly(esters)[a]

polymer	depolymerization[b] rate constant (t^{-1})					actn energy, kcal/(mol K)
	−20 °C	0 °C	21 °C	37 °C	45 °C	
poly(SA)	0.0071	0.0324	0.0763	0.1325	0.2247	8.08
poly(CPP:SA) 20:80	0.0077	0.0251	0.0777	0.1535	0.2254	8.27
poly(CPP:SA) 50:50	0.0006	0.0041	0.0395	0.0743	0.1014	7.27[c]
poly(CPH)	0.0000	0.0000	0.0000	0.0000	0.0000	
poly(CPM)	0.0000	0.0000	0.0000	0.0000	0.0000	
poly(orthoester)-A	0.0000	0.0000	0.0041	0.0082	0.0108	7.56[c]
poly(orthoester)-B	0.0000	0.0000	0.0039	0.0080	0.0100	7.43[c]
poly(LA)	0.0000	0.0000	0.0000	0.0000	0.0000	
poly(LA-GA)	0.0000	0.0000	0.0000	0.0000	0.0000	
poly(ES)	0.0000	0.0000	0.0000	0.0000	0.0000	

[a] Depolymerized in chloroform solution (10 mg/mL); depolymerization was followed by viscosity measurements at 23 °C for 24 h. [b] Calculated on the basis of first-order kinetics. [c] Determined from the rate constants at 21, 37, and 45 °C.

Stability of Poly(anhydrides) in Solution. The stability of poly(anhydrides) in chloroform solutions is demonstrated in Figure 3.

The decrease in molecular weight of aliphatic poly(anhydrides) in solution was higher than in the bulk, while for aromatic poly(anhydrides), the molecular weight remained unchanged. Copolymers of CPP and SA possessed depolymerization rates that depended upon aromatic content. Increasing the relative amount of aromatic comonomer (CPP) stabilizes the polymers. The depolymerization in chloroform at various temperatures is de-

---

* To whom correspondence should be addressed.

[†] Current address: Nova Pharmaceuticals, Baltimore, MD.

0024-9297/89/2222-2117$01.50/0 © 1989 American Chemical Society

Table II
Analytical Data of Poly(sebacic anhydride) Depolymerized in Chloroform

property	original	depolymerized
M_w (GPC)	137 000	13 500
M_n (GPC)	20 700	4300
$[\eta]$ (23 °C, $CHCl_3$), dL/g	0.98	0.21
mp, °C	81–83	66–68
IR (film on NaCl plates), cm^{-1}	1800, 1740	1805, 1740 ("fingerprint" identical with original)
^1H NMR ($CDCl_3$, TMS), ppm	1.32 (br s, 8 H), 1.65 (br, 4 H), 2.45 (t, 4 H, J = 2.4 Hz)	1.34 (br s, 8 H), 1.67 (br, 4 H), 2.45 (t, 4 H, J = 2.4 Hz)
^{13}C NMR ($CDCl_3$), ppm	24.33 (2 CH_2), 28.72 (2 CH_2), 28.94 (2 CH_2), 35.25 (2 CH_2), 169.50 (2 COO)	24.35 (2 CH_3), 28.76 (2 CH_2), 28.94 (2 CH_2), 35.23 (2 CH_2), 169.47 (2 COO)
elem anal., %	C, 65.22; H, 8.81; O, 25.52	C, 65.64; H, 8.85; O, 25.68
calcd for $C_{10}H_{16}O_3$, %	H, 8.69; O, 26.08	

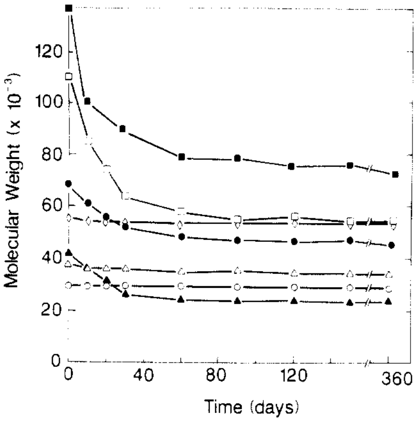


Figure 1. Solid-state depolymerization of poly(anhydrides). Weight average molecular weight of bulk poly(anhydrides) stored under vacuum at 21 °C as determined by GPC: ■ poly(SA); □ poly(CPP:SA) 20:80; ● poly(CPP:SA) 35:65; ◇ poly(CPP:SA) 50:50; ○ poly(CPH); ▲ poly(PDP); △ poly(CPM).

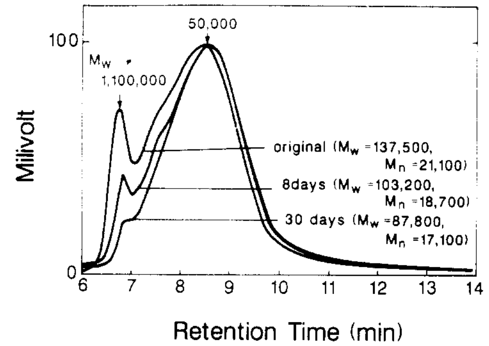


Figure 2. Solid-state depolymerization of poly(anhydrides), GPC output. Poly(SA) stored under vacuum at 21 °C.

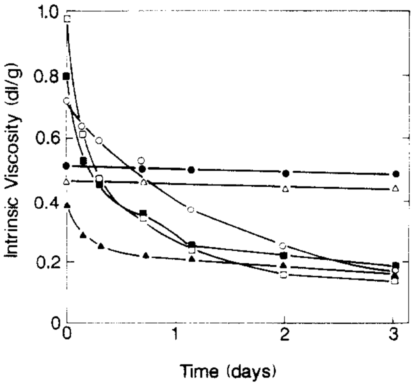


Figure 3. Solution depolymerization of poly(anhydrides). Poly(anhydrides) in chloroform (10 mg/mL) stored under nitrogen at 37 °C: □ poly(SA); ■ poly(CPP:SA) 20:80; ○ poly(CPP:SA) 50:50; △ poly(CPH); ● poly(CPM); ▲ poly(PDP). Viscosity was measured at 23 °C.

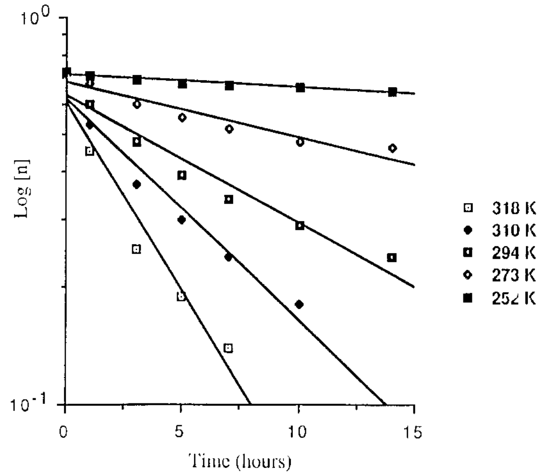


Figure 4. Depolymerization of poly(sebacic anhydride) in chloroform at various temperatures. Polymer solutions (10 mg/mL) stored at specified temperatures. Viscosity was measured at 23 °C.

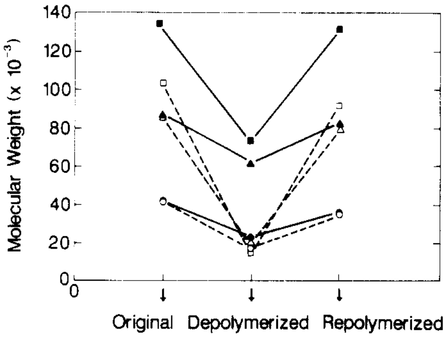


Figure 5. Repolymerization of poly(anhydrides). Repolymerization at 180 °C for 20 min of poly(anhydrides) depolymerized in bulk (21 °C for 2 months, solid line) or solution (chloroform, 10 mg/mL, 21 °C for 48 h, dashed line): ■, □ poly(SA); ▲, △ poly(CPP:SA)35:65; ●, ○ poly(PDP).

scribed in Figure 4. Increased temperature resulted in increased depolymerization. The depolymerization data follow first-order kinetics (correlation coefficient > 0.97). The depolymerization rate constants and the corresponding activation energies of several poly(anhydrides) are summarized in Table I. Activation energies of 7.5 kcal·mol^{-1} were obtained for poly(anhydrides), which is typical for a reaction proceeding at room temperature.[13] As seen in this table, minimal depolymerization takes place at temperatures below 0 °C, which indicates that storage below 0 °C is an advantage for long-term polymer stabilization.

Elemental analysis of the products of the depolymerization in both solid state and solution was equivalent to that for the respective original polymers. In addition, IR and NMR (^{13}C, ^1H) spectra analysis revealed a similarity between depolymerization products and their higher molecular weight counterparts (Table II). Finally repolymerization of the depolymerization products yielded

Table III
Solution Depolymerization in the Presence of ^3H_2O[a]

polymer	mol wt original M_n	 M_u[b]	 Dp[c]	 depolymerized M_n	 Dp[c]	^3H_2O reacted[d] if hydrolyzed, mol	radioactivity, cpm expected[d]	 found[g]
poly(AA)	4580	128	35.8	1238	9.7	1.47×10^{-4}	1.47×10^{6}	42
poly(SuA)	19174	156	122.9	5600	35.9	3.14×10^{-5}	3.14×10^{5}	73
poly(SA)	18960	184	103.0	6550	35.6	2.01×10^{-5}	2.01×10^{5}	48
poly(CPP-SA) 2.0:80	20180	206.8	97.6	8830	42.7	1.54×10^{-5}	1.54×10^{5}	81
poly(CPP-SA)[e] 20:80	20180	206.8	97.6	2480	12.0	8.81×10^{-5}	8.81×10^{5}	155
poly(orthoester)-A[f]	0.75			0.48				145

[a] Polymer solution (0.25 g in 50 mL of chloroform) containing 100 μL of ^3H_2O (1 mCi/g) stored at 40 °C with constant stirring for 24 h. Molecular weight was determined by GPC. [b] M_u is the molecular weight of repeating unit of the polymer. [c] Calculated from M_n/M_u. [d] See calculation method in the Experimental Section. [e] Depolymerized in THF at 40 °C for 2 h. [f] Molecular weight determined by intrinsic viscosity. [g] Reference experiment without polymer was counted at 22–56 cpm.

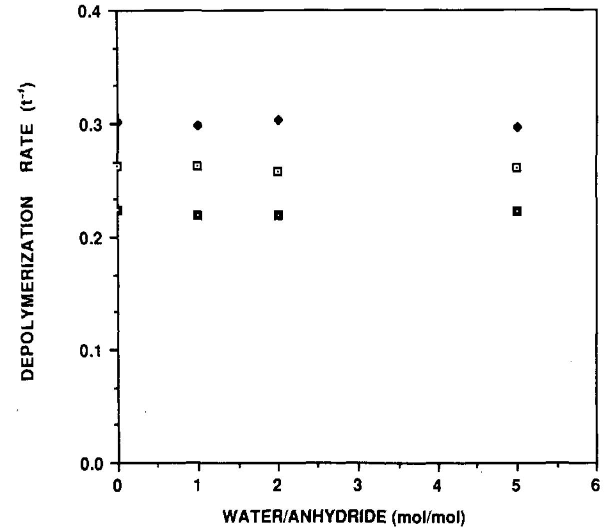


Figure 6. Solution depolymerization in the presence of water. Polymer solutions in chloroform (0.5% w/v) containing 1–3 times molar excess of water were depolymerized at 40 °C: ◆ poly(AA); ▣ poly(SuA); ■ poly(CPP-SA) 20:80.

polymers with the initial M_w (Figure 5). These data suggest a self-depolymerization process via inter- and/or intramolecular anhydride interchange resulting in ring formation (Scheme I). Similar mechanisms were suggested in the thermal decomposition of several polymers including poly(anhydride).[3,9] Alternatively, one might suggest a hydrolysis process rather than self-depolymerization. If this were the case, solution depolymerization in the presence of increasing concentrations of water in polymer solution should increase the depolymerization rate, and by extrapolating to zero water concentration, the pure self-depolymerization rate could be determined (e.g., the intercept). In addition, a radiolabeled polymer would be expected when depolymerization was conducted in the presence of radiolabeled water (^3H_2O). The depolymerization rates of several polyanhydrides in chloroform solution containing an increased concentration of water is shown in Figure 6. The depolymerization rate was not affected by water, although excess water (water/anhydride 5:1 molar ratio) was used. Spectral analysis (^1H NMR, IR) revealed no changes in polymer analysis for the 24 h of the study. The results on solution depolymerization, in the presence of ^3H_2O are described in Table III. All polymers exhibited no radioactivity, although high radioactivity was expected if hydrolysis occurred (Table III). These data, in addition to the data described above (Tables II and VI and Figure 5) on the similarity between the depolymerization product and the original polymer and the reversibility of the depolymerization process, strongly suggest an exclusive self-depolymerization process in solution during the period of study. For comparison, when poly(SA) (M_w = 121 000) was partially hydrolyzed by exposing the polymer powder to air moisture (70% humidity) for 7 days, major changes were observed: (1) the polymer was partially soluble in chloroform; (2) the soluble fraction had a weight average molecular weight of 31 400; (3) IR spectra revealed the formation of carboxylic acid groups (appearance of a new peak at 1720 cm^{-1}); the product had a melting range of 77–110 °C; (4) repolymerization of the degradation products (180 °C for 20–300 min) did not affect product properties such as molecular weight.

Table IV
Concentration Effect on Depolymerization of Poly(SA) in Chloroform[a]

concn, mg/mL	M_w	M_n	[η]
0.1	6400	970	0.12
0.1[b]	850	570	
1	12490	1604	0.17
10	18700	2850	0.23
50	28275	4549	0.36
100	37435	6910	0.42

[a] Solutions of poly(SA) of 99 400 (M_w), 17 900 (M_n), and [η] = 0.85 dL/g were stored at 37 °C for 24 h. The molecular weight (M_w, weight average; M_n, number average) was determined by GPC; viscosity was measured at 23 °C. [b] Depolymerized in the presence of zinc powder (10 mg/mL).

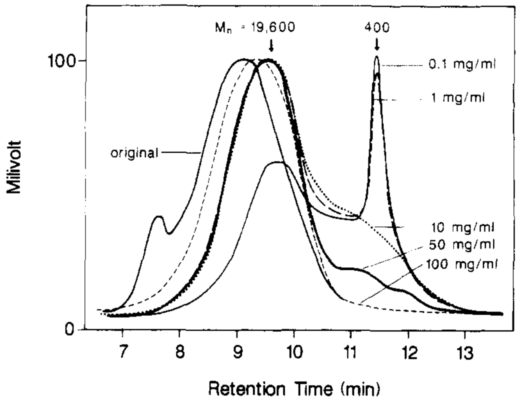


Figure 7. Concentration effect on depolymerization of poly(sebacic anhydride) in chloroform, GPC output. Solutions of poly(SA) of 99 400 (M_w), 17 900 (M_n), and [η] = 0.85 dL/g were stored at 37 °C for 24 h.

According to the proposed self-depolymerization mechanism, higher dilutions of polymer in solvent should increase the relative probability of intramolecular reaction.[14] Indeed, depolymerization at low concentrations of poly(SA) or poly(PDP) resulted in the emergence of a low molecular weight fraction (M_n = 400) which was attributed to the formation of cyclic dimers. Increasing the concentration of the polymer inceased its stability (Table IV and Figure

Scheme I

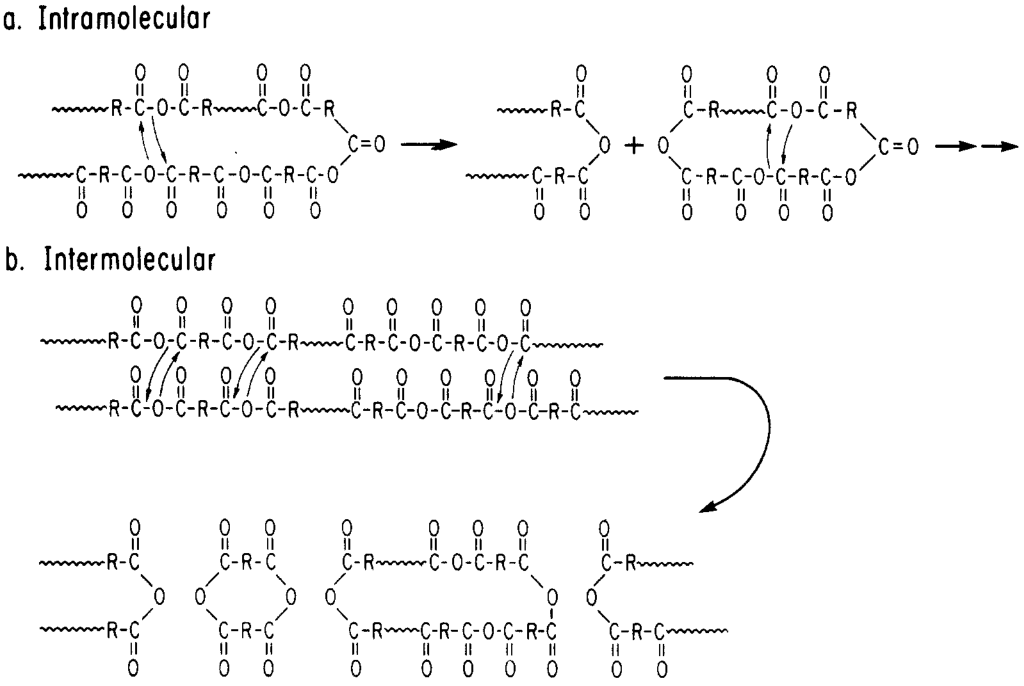


Table V
Solution Depolymerization of SA, PDP, and CPH Polymers: Metal Catalysis[a]

	poly(S)		poly(PDP)		poly(CPH)	
cat./polym	M_w	M_n	M_w	M_n	M_w	M_n
original polym	137 800	21800	43 000	4200	30 100	10800
no metal	45 255	9055	19 600	2100	30 100	10600
palladium	46 400	8750	15 900	1910	28 900	9400
zinc	5 156	1690	3 850	1100	24 600	8450
copper	6 122	1532	3 180	1150	25 300	8350
iron	41 507	6692	18 400	1690	29 800	9600
nickel	47 200	9850	19 100	2310	30 200	10100
tin	46 400	9390	17 600	2100	30 510	9480
aluminum	48 300	8900	18 500	1910	29 600	9990

[a] Solutions of polymers (10 mg/mL) and metal powders (10 mg/mL) in chloroform were allowed to react at 37 °C for 24 h. The molecular weight (M_w, weight average; M_n, number average) was determined by GPC.

7). The depolymerization was solvent dependent. Following the molecular weight (by GPC) of poly(CPP:SA) 20:80 and 50:50 in tetrahydrofuran showed a decrease in molecular weight from 74 900 and 51 700 to 15 220 and 16 890, respectively, after 1 h at 37 °C. This was faster than the depolymerization in chloroform, which showed a decrease to 62 000 and 44 600, respectively, under the same conditions. The depolymerization in tetrahydrofuran was presumably a self-depolymerization process as revealed from the similarity between the depolymerization products and the original polymer (determined by IR, ^{1}H, ^{13}C NMR, spectroscopy, and elemental analysis) and the reversibility of the process. In addition depolymerization in the presence of radiolabeled water (^3H_2O/anhydride 5:1 molar ratio) did not affect depolymerization rate and showed spectral analysis (IR, ^{1}H NMR) identical with the original polymer, and the isolated depolymerization products were not radiolabeled (Table III), although a sharp decrease in molecular weight was observed [original polymer M_w = 106 640, Mn = 18 288; depolymerized polymer (2 h at 40 °C) M_w = 7194, M_n = 3645]. The higher depolymerization rate in tetrahydrofuran is attributed to the increase in solvent polarity, which might catalyze the anhydride interchange.

The depolymerization process in solution could be catalyzed by metals. Among the metals tested (palladium, iron, zinc, copper, nickel, tin, and aluminum), zinc and copper were the most effective (Table V). While the depolymerization of both aliphatic and aromatic polymers could be effected by metal catalysts, the aromatic polymers studied (poly(CPH) and poly(CPM)) were more stable. It is likely that interaction of anhydride bonds with the metal weaken the anhydride bond and facilitated an anhydride interchange.

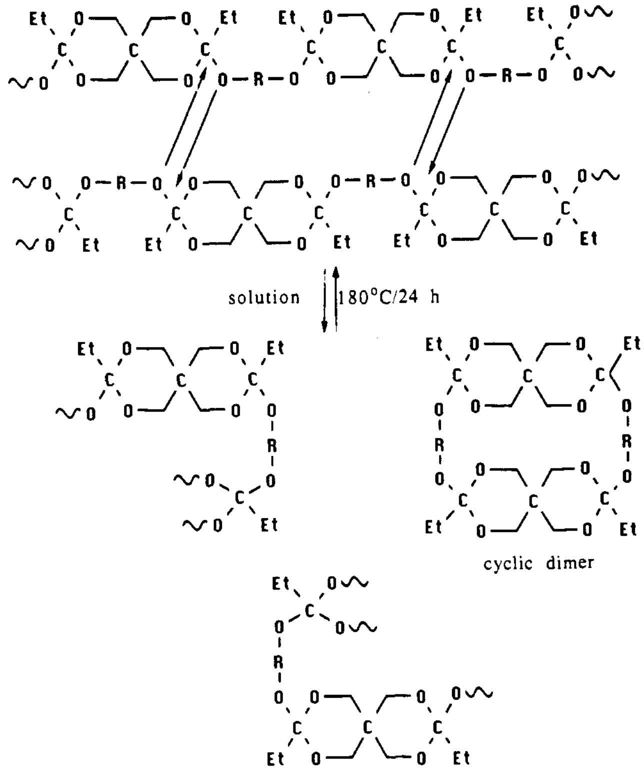
Stability of Poly(esters) in Solution. Similar studies were performed on the stability of aliphatic poly(esters) in organic solvents. These polymers were reported to undergo thermal depolymerization via internal ester exchange[9] as do the poly(anhydrides)[3] and thus might exhibit similar instability in solution. The following polymers were tested: poly(orthoester)-A and -B (see Experimental Section) poly(lactic acid) (poly(LA)), poly(lactic-*co*-glycolic acid) (poly(LA-GA)), and poly(ethylenesuccinate) (poly(ES)). The poly(orthoesters) studied decreased in viscosity over time, while the other poly(esters) remained intact. The decrease in molecular weight is temperature dependent. At temperatures below 0 °C the polymers were stable. The depolymerization rates of these polymers are described in Table I. The depolymerization products displayed elemental analysis and IR and ^{1}H and ^{13}C NMR spectra identical with the respective original polymer (Table VI). Furthermore, repolymerization of the depolymerization products yielded the high molecular weight polymer (see Experimental Section). These data suggest a self-depolymerization process via inter- and/or intramolecular ester interchange resulting in ring formation (Scheme II). The data cannot be explained by hydrolysis because poly(orthoesters) are relatively stable toward hydrolysis[11,12] and they degrade into alcohols which are inactive in orthoester melt polymerization. As shown in Table VI, a sharp decrease in molecular weight was observed, which must affect elemental and spectral analysis if new functional groups are produced.

The data discussed here revealed the instability of the two types of polymers, poly(anhydrides) and poly(orthoesters); it is possible that other types of polymers (e.g.,

Table VI
Analytical Data of Poly(orthoester)-A Depolymerized in Chloroform

property	original	depolymerized
[η] (23 °C, $CHCl_3$), dL/g	0.75	0.09
mp, °C	125	<20
IR (film on NaCl plates), cm^{-1}	2940, 2860, 1460	2940, 2860, 1460 ("fingerprint" identical with original)
^1H NMR ($CDCl_3$, TMS), ppm	0.93 (t, 6 H, J = 7.3 Hz), 1.77 (q, 4 H, J = 7.3 Hz), 1.44–2.37 (m, 8), 3.21–4.17 (m, 12)	0.93 (t, 6 H, J = 7.3 Hz), 1.77 (q, 4 H, J = 7.3 Hz), 1.44–2.37 (m, 8), 3.21–4.17 (m, 12) (identical with original)
^{13}C NMR ($CDCl_3$), ppm	112.7, 77.2, 71.0, 70.5, 67.8, 63.1, 62.4, 38.4, 30.7, 29.9, 28.5, 26.4	112.7, 77.2, 71.0, 70.5, 67.8, 63.1, 62.4, 38.4, 30.7, 29.9, 28.5, 26.5
elem anal., %	C, 60.80; H, 8.77; O, 31.21	C, 60.42; H, 8.58; O, 30.95
calcd for $C_{16.8}H_{28.9}O_6$, %	C, 61.74; H, 8.85; O, 29.40	

Scheme II



R= $(CH_2)_6$, $(CH_2)_4$, CH_2-C_6H_{10}-CH_2

poly(ketones), poly(carbonates)[9] exhibit similar phenomena. The thermodynamic instability is not correlated to the hydrolytic instability of the polymers, because in aqueous solution at neutral pH poly(lactic acid) degrades faster than poly(orthoesters),[10,11] and for the poly(anhydrides), poly(CPM) degrades faster then poly(CPP:SA) 50:50 (2 weeks[3] vs a few months[7]); yet, poly(CPM) is stable in organic solution. However, for the poly(anhydrides) studied, copolymers of CPP:SA that exhibited higher stability in both solid state and solution also had higher hydrolytic stability.[4,5]

In summary, this study reveals a general phenomenon of thermodynamical instability of several classes of polymers in solid state and in solution under inert conditions, at ambient temperatures. These findings might have theoretical and practical implications. The practical importance of this discovery is that in the field of biomaterials, such changes in polymer properties with time may affect their potential applications and workup. For example, in drug delivery systems based on self-depolymerizing polymers, such changes may alter their drug release properties with time. In the manufacturing step where polymer solutions are used for film casting or microencapsulation, a possible decrease in polymer molecular weight with time should be taken into consideration. Future studies will focus on a thermodynamic analysis to obtain a better understanding of self-depolymerization phenomena.

Experimental Section

General Methods. Poly(anhydrides) were synthesized as previously described by melt polycondensation.[16] Poly(DL-lactic acid) and poly(DL-lactic-*co*-glycolic acid) were purchased from Polysciences, (Warrington, PA); poly(orthoesters), copolymers of diketene acetal, 3,9-bis(ethylidine)-2,4,8,10-tetraoxaspiro-[5.5]undecane, *trans*-cyclohexanedimethanol, 1,6-hexanediol, and 1,4-butanediol, in molar ratio 1:0.35:0.20:0.45 (polyorthoester)-A or 1:0.35:0.50:0.15 (polyorthoester)-B were synthesized according to Heller.[11,12] Metal powders zinc, copper, nickel, iron, tin, aluminum, and palladium of particle size less than 50 μm, were from Aldrich Chemical Co. (Milwaukee, WI). Metals were washed with acetone and chloroform and dried at 50 °C under nitrogen prior to use. Anhydrous chloroform (Aldrich, water < 0.005%) was dried over activated alumina and freshly distilled under nitrogen before use. Anhydrous tetrahydrofuran (Aldrich, water < 0.005%) was dried over sodium benzophenone ketyl and freshly distilled. All experiments were performed in triplicate under anhydrous conditions, unles otherwise specified. ^3H_2O (1 mCi/g) and scintillation fluid (Aquasol) were from New England Nuclear (Boston, MA). Elemental analyses were performed by Galbraith Laboratories (Knoxville, TN). Thermal analysis of the polymers and depolymerization products was determined on a Perkin-Elmer DSC-2 differential scanning calorimeter, employing a heating rate of 20 °C/min, and by a Fisher-Johns melting point apparatus. IR spectroscopy was performed on a Perkin-Elmer Series 1420 dispersive spectrophotometer.

The molecular weight of polymers was determined relative to polystyrene standards in chloroform solutions (10 mg/mL) by gel permeation chromatography (GPC) on a Perkin-Elmer instrument equipped with a LKB-2140 diode array multiple-wavelength UV detector. Two Perkin-Elmer PL-gel (10 μm) columns (exclusion limits: 300–1 500 000), connected in series, were used. The flow rate was 1.5 mL/min. Low-concentration samples (<10 mg/mL) were detected after concentration by evaporation under nitrogen at 20 °C.

Intrinsic viscosity measurements were performed on a Ubbelohde viscometer (50 μm, Cannon, PA) at 23 °C in chloroform. When lower or higher concentrations were determined, the concentration was adjusted to 1% by evaporation or dilution at room temperature under argon.

^{13}C and ^1H NMR spectra were obtained on a Varian 270-MHz NMR spectrometer with deuterated chloroform as a solvent and tetramethylsilane (TMS) as an internal reference. Samples were counted for radioactivity by a Packard TRT–CARB 4530 (Packard, VA).

Depolymerization Studies. Bulk poly(anhydrides) immediately after synthesis were stored in dry glass ampules (0.25 g of polymer in a 1-mL volume) and sealed under vacuum or dry argon. At each time point, the contents of three ampules were analyzed separately and the average molecular weight was given. Solution depolymerization was performed in either chloroform or tetrahydrofuran using sealed glass vials with constant shaking.

Kinetic studies on the depolymerization at various temperatures were performed as follows: 100 mL of chloroform solution of polymers (10 mg/mL) was stored at the appropriate temperature, and the decrease in molecular weight with time was followed by viscosity measurements at 23 °C. Results are a mean of eight experiments. Results were interpreted as first-order kinetics.

When metal catalysts were used, 100 mg of metal powder was added to a 10-mL solution of 10 mg/mL of polymer in chloroform. In a typical experiment poly(SA) in chloroform (10 mg/mL) was placed in a 37 ± 0.5 °C oven for 24 h. Aliquots were removed at different time points for GPC and viscosity measurements. The solution was evaporated to dryness at 10 °C under nitrogen, and the residue was analyzed by NMR (^{13}C, ^{1}H), IR spectroscopy, melting point, and elemental analysis. The analytical data for the original and depolymerized polymers are summarized in Table II.

For the depolymerization of poly(orthoesters), poly(orthoester)-A in chloroform (10 mg/mL) was depolymerized at 37 °C for 72 h. After solvent evaporation the liquid residue was analyzed as above. The analytical data for the original and depolymerized polymers are summarized in Table VI.

Solution Depolymerization in the Presence of Water. To chloroform solutions (10 mL, 0.5% w/v) of poly(adipic anhydride), poly(suberic anhydride), and poly(sebacic anhydride), increased amounts of water (0–50 μL) were added and stored at 40 °C with constant stirring. Changes in the polymer with time were followed by IR and GPC. Results were interpreted as first-order kinetics for the first 4 h of depolymerization. Depolymerization in THF was performed in the presence of 5:1 molar excess of water to anhydride bonds in the samples. When radioactive water was used, 100 μL of $^{3}H_2O$ (1 mCi/g) was added to 50 mL of polymer solution (0.5% w/v) and stored as above for 24 h. The solution was concentrated to 5 mL (under nitrogen stream) and poured in excess petroleum ether. The precipitate was purified twice by precipitation in petroleum ether from chloroform solution. The purified polymer was dissolved in 1 mL of chloroform and mixed with scintillation fluid and counted for radioactivity. The expected radioactivity of the polymers if hydrolyzed was calculated as follows: The number of anhydride bonds in 0.25 g of polymer is (in moles)

$$0.25/M_n(\mathrm{Dp} - 1) \qquad (1)$$

The amount of lost anhydride bonds in 0.25 g of polymer (which is equal to the expected amount of $^{3}H_2O$ (in moles), reacted with the polymer) if hydrolyzed is

$$0.25/M_{n_o}(\mathrm{Dp}_o - 1) - 0.25/M_{n_d}(\mathrm{Dp}_d - 1) \qquad (2)$$

where M_{n_o} and M_{n_d} are the number average molecular weight of the original and the depolymerized polymer respectively. Dp is M_n/M_u where M_u is the molecular weight of the repeating unit in the polymer. The expected radioactivity (in cpm) was calculated from the result of eq 2 multiplied by the radioactivity (in cpm) of 1 mol of the $^{3}H_2O$ used. In our experiments, the $^{3}H_2O$ (1 mCi/g) was counted at 1.0×10^{10} cpm/mol.

Repolymerization of Depolymerization Products. Depolymerization products of poly(anhydrides) from the solid state or from solution depolymerization were polymerized at 180 °C under vacuum for 20 min. Depolymerization products of poly(orthoesters) were repolymerized at 180 °C for 24 h. For the polymers described above, the repolymerized poly(SA) had the following analytical data: molecular weight M_w = 120 100, M_n = 20 800, [η] = 0.89 dL/g, melting point, 81–83 °C. Elemental analysis: C, 65.34, H, 8.84, O, 25.37 (calcd for $C_{10}H_{16}O_3$: C, 65.21; H, 8.69; O, 26.08). NMR (^{13}C, ^{1}H) and IR spectra were identical with the original polymer. Poly(orthoester)-A had [η] = 0.45 dL/g, melting point 123–128 °C. Elemental analysis: C, 60.73; H, 8.67; O, 31.05 (calcd for $C_{16.8}H_{28.9}O_6$: C, 61.74; H, 8.85; O, 29.40). NMR (^{13}C, ^{1}H) and IR spectra were identical with the original polymer.

Acknowledgment. This study was supported by GM 26698 and a gift from Nova Pharmaceuticals. We thank Dr. Jorge Heller of SRI International for his generous gift of poly(orthoesters) and Dr. Eyal Ron for his help in writing the manuscript.

Registry No. SA (homopolymer), 26776-29-4; SA (SRU), 26913-47-3; (CPP)(SA) (copolymer), 90409-78-2; CPH (homopolymer), 106680-96-0; CPH (SRU), 118418-96-5; CPM (homopolymer), 86468-47-5; CPM (SRU), 118418-97-6; LA (homopolymer), 31587-11-8; LA (SRU), 118418-98-7; (LA)(GA) (copolymer), 59199-59-6; ES (homopolymer), 25569-53-3; ES (SRU), 25667-11-2; Pd, 7440-05-3; Zn, 7440-66-6; Cu, 7440-50-8; Fe, 7439-89-6; Ni, 7440-02-0; Sn, 7440-31-5; Al, 7429-90-5; H_2O, 7732-18-5; (3,9-bis(ethylidene)-2,4,8,10-tetraoxaspiro[5.5]undecane)(*trans*-cyclohexanedimethanol)(1,6-hexanediol)(1,4-butanediol) (copolymer), 118418-95-4.

References and Notes

(1) Grassie, N. *Development in Polymer Degradation*; Applied Science: London, 1977; Vol. 1–6.
(2) Jellinek, H. H. G. *Degradation and Stabilization of Polymers*; Elsevier: New York, 1983.
(3) Hill, J. W.; Carothers, W. H. *J. Am. Chem. Soc.* **1932**, *54*, 1969.
(4) Yoda, N. *Kogyo Kagku Zasshi* **1962**, *65*, 673.
(5) Leong, K. W.; Brott, B. C.; Langer, R. *J. Biomed. Mater. Res.* **1985**, *19*, 941.
(6) Rosen, H. B.; Chang, J.; Wnek, G. E.; Linhardt, R. J.; Langer, R. *Biomaterials* **1983**, *4*, 131.
(7) Mathiowitz, E.; Saltzman, W. M.; Domb, A. J.; Dor, Ph.; Langer, R. *J. Appl. Polym. Sci.* **1987**, *35*, 755.
(8) Leong, K. W.; Simonte, V.; Langer, R. *Macromolecules* **1987**, *20*, 705.
(9) Thermal depolymerization and ring formation was reported also. Poly(esters): Carothers, W. H.; Dorough, G. L.; Van Natta, F. J. *J. Am. Chem. Soc.* **1933**, *55*, 5043. Nisso, P. *Jpn. Kokai Tokyo Koho* **1982**, *57*, 122, 078. Poly(ketones): Carothers, W. H.; Hill, J. W. *J. Am. Chem. Soc.* **1933**, *55*, 5043. Poly(carbonates): Sarel S.; Poyoryles, L. A. *J. Am. Chem. Soc.* **1958**, *80*, 4597. Poly(dimethylsiloxanes): Thomas T. H.; Kendrick, T. C., *J. Polym. Sci., Polym. Phys. Ed.* **1969**, *7*, 537.
(10) Kopecek, J.; Ulbrich, K. *Prog. Polym. Sci.* **1983**, *9*, 1.
(11) Heller, J. *J. Controlled Release* **1985**, *1*, 225.
(12) Heller, J. *J. Controlled Release* **1985**, *1*, 233.
(13) Levenspiel, O. *The Chemical Reactor Omnibook*: OUS Book Stores: Corvallis, OR 1979; pp, 1–4.
(14) Rugglie, Cf. *Annu.* **1912**, *92*, 392.
(15) Spanagel, E. W.; Carothers, W. H. *J. Am. Chem. Soc.* **1935**, *57*, 929.
(16) Domb, A. J.; Langer, R. *J. Polym. Sci.* **1987**, *25*, 3373.