Synthesis and Properties of Polyanhydrides Containing Urethane Bonds in the Main Chain†

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SYNTHESIS AND PROPERTIES OF POLYANHYDRIDES CONTAINING URETHANE BONDS IN THE MAIN CHAIN†

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ABSTRACT

Polyanhydrides containing urethane linkages in the main chain have been synthesized from bis(4-carboxyphenyl-amino-carbonyloxy) alkanes and oxyalkanes by melt polycondensation of the corresponding acetic mixed anhydrides. Weight-average molecular weights up to 27,000 were obtained. All polymers have been characterized by ^{1}H-NMR and IR spectroscopy as well as by TG analysis. The dicarboxylic acid monomers were prepared by reaction of 4-aminobenzoic acid with suitable bis(chloroformate)s. Hydrolysis of the synthesized polyanhydrides (pH 7.4; 37°C) proceeds with cleavage of anhydride bonds and maintenance of urethane linkages to give nearly constant degradation rates. Comparative hydrolysis studies including poly(amide-anhydride)s and poly(ester-anhydride)s having analogous structures are described. The release of 4-nitroanisole as a drug model from a polyanhydride matrix followed the polymer degradation to a large extent.

INTRODUCTION

Polyanhydrides which have both aromatic and aliphatic moieties in the main chain are of particular interest as polymers for application in drug delivery systems due to their biodegradability [1–4]. Previous publications from our laboratory re-

†Dedicated to Otto Vogl on the occasion of his 65th birthday.

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ported the synthesis and characterization of polyanhydrides containing amido groups [5, 6] or ester groups [7] as well as alkylene and oxyalkylene units, respectively, in the polymer backbone. These polymers with different hydrolytically cleavable bonds were prepared by using the method of polycondensation of the corresponding diacids via acetic mixed anhydrides [8]. Weight-average molecular weights of up to 17,900 were obtained.

The objectives of this work were to prepare novel polyanhydrides having urethane bonds in the main chain and to study the hydrolytic degradation of these polymers in dependence of the polymer structure and in comparison with the degradation of analogous poly(amide-anhydride)s and poly(ester-anhydride)s which were previously described [6, 7]. In addition, the release of the model drug 4-nitroanisole from a selected poly(amide-anhydride) has been studied.

EXPERIMENTAL

Materials

Ethylene glycol (Ia), 1,4-butanediol (Ib), diethylene glycol (Ic), triethylene glycol (Id), and tetraethylene glycol (Ie) were obtained from E. Merck (Germany) and purified by vacuum distillation. 4-Aminobenzoic acid (ABA) and 4-nitroanisole (NA) were purchased from Laborchemie Apolda (Germany) and recrystallized twice from water (ABA; mp 187°C) and ethanol-water (NA; mp 54°C), respectively. 4-Hydroxybenzoic acid (HBA; mp 214°C) (from Merck) was recrystallized from water and then from xylene–ethanol. Trichloromethyl chloroformate (Disphosgene, Aldrich) and bis(trichloromethyl)carbonate (Triphosgene, Merck) were used as received. All solvents were purified by standard methods.

Monomer Synthesis

Bis(chloroformate)s (IIa–IIe)

To a solution of 62.5 mmol diphosgene or 41.7 mmol triphosgene in 60 mL tetrahydrofurane (THF), 50 mmol of the diol (Ia–Ie) dissolved in 20 mL THF, and 15.0 g charcoal activated (powder extra pure from Merck) were added simultaneously with stirring and ice cooling during an 8-h period. The temperature of the reaction mixture should not exceed 5°C. After stirring was continued for 24 h at room temperature, a violent stream of dry argon was bubbled through the mixture for 15 min. To remove the charcoal the solution was filtered through cellulose powder (type FND for TLC from FILTRAK). The solvent was removed by distillation under reduced pressure to yield 89–98% of a yellow liquid. The crude products of IIa–IIe thus obtained decompose at higher temperatures; therefore they could not be purified by distillation before analysis. However, in accordance with the literature [9–11], they were pure enough for the following acylation reactions.

Bis(4-carboxyphenyl Urethane)s (IIIa–IIIe)

47.0 mmol of the corresponding bis(chloroformate) (IIa–IIe) dissolved in 20 mL THF was added to a solution of 13.5 g (94 mmol) 4-aminobenzoic acid (ABA) in 70 mL absolute pyridine with stirring at 0°C. After stirring at room temperature for a further 6 h, the reaction mixture was poured onto 500 g ice and acidified with

concentrated HCl to pH 2.0. The solid material was filtered off, washed with cold water, dried, and recrystallized from dioxane-water (IIIa) or ethanol-water (IIIc, IIId, IIIe). IIIb was purified by extraction with methanol. IIIc could also be synthesized using the Schotten–Baumann condensation of ABA and IIc in 2 M NaOH at room temperature. The yield, the elemental analysis, and the spectroscopic data of the synthesized urethanes are presented in Table 1.

Acetic Mixed Anhydrides (IVa–IVe)

These compounds were prepared as previously described [5-7]. Their properties are listed in Table 2.

Synthesis of Polyanhydrides (Va–Ve)

The polycondensation of the acetic mixed anhydrides IVa–IVe was carried out analogously to Procedure C described in Ref. 6. The conditions of these polycondensation reactions as well as the properties of polymers formed are given in Table 3. At the end of the polycondensation the crude materials were dissolved in DMF (Va, Vb) or in THF (Vc, Vd, Ve), and precipitated in a large excess of acetone (Va, Vb), or hexane (Vc), or acetic acid ethyl ester (Vd, Ve). Then the polymers were dried in vacuum at room temperature.

Hydrolytic Degradation of Polyanhydrides and Release of 4-Nitroanisole

Disk-shaped samples of 100–300 mg polymer, 18 mm in diameter and approximately 1 mm thick, were prepared by compression molding with a homemade apparatus [12, 13]. The hydrolysis was performed in a phosphate buffer system at pH 7.4 and 37°C with magnetic stirring. The degradation rate was determined by the mass loss of the polymer samples in definite time intervals. The hydrolysis was qualitatively followed both by measurement of the UV absorbance of the solution at 266 nm (ABA), 259 nm (IIId), and 251 nm (HBA), as well as by IR spectroscopy of the products isolated after acidification of the hydrolysis solution with HCl.

4-Nitroanisole (NA) powder was mixed (10% w/w) with the polymer before compression molding. Samples of 5 mL were removed from the solution through a filter appliance in appropriate periods, and an equivalent volume of water was returned. This change of concentration was taken into consideration in quantitative analysis. The amount of NA released from the polymer matrix was measured by UV spectroscopy at 317 nm (E = 0.1–2.0; ϵ = 10667 L/mol·cm).

Measurements

Nitrogen data were determined volumetrically by using the method of Dumas. IR spectra were obtained with a Carl Zeiss Jena spectrometer M 80 with pressed KBr pellets. ^{1}H-NMR analysis were performed in DMSO-d_6 and hexamethyldisiloxane as internal standard either with a Bruker WP 200 SY or a Tesla B 287 spectrometer. The UV spectra were measured with a Specord M 40 from Carl Zeiss Jena. The number-average molecular weights of polymers were determined by vapor-pressure

TABLE 1. Yields and Characterization of Bis(4-Carboxyphenyl Urethane)s (IIIa–IIIe)

Compound III	Yield, %	mp, °C	Brutto formula (molecular weight)	Analysis, N, %		IR data, in cm^{-1}				^{1}H-NMR data, δ in ppm		
				Calcd.	Found	ν_{NH}	$\nu_{C=O}$ (urethane)	$\nu_{C=O}$ (acid)	δ_{NH}	NH	OCO—CH$_2$	Ether CH$_2$
a	55	273 (dec.)	C$_{18}$H$_{16}$N$_2$O$_8$ (388.3)	7.21	7.11	3345	1715	1685	1540	10.24	4.51	—
b	62	287 (dec.)	C$_{20}$H$_{20}$N$_2$O$_8$ (416.4)	6.72	6.50	3344	1712	1680	1530	10.02	4.16	(1.74)[b]
c	83[a]	263–265	C$_{20}$H$_{20}$N$_2$O$_9$ (431.4)	6.49	6.90	3320	1710	1690	1536	10.32	4.46	3.91
d	50	207	C$_{22}$H$_{24}$N$_2$O$_{10}$ (476.3)	5.88	5.42	3328	1712	1688	1534	10.09	4.25	3.67 3.59
e	33	139	C$_{24}$H$_{28}$N$_2$O$_{11}$ (520.5)	5.38	5.11	3308	1716	1692	1538	10.10	4.20	3.65 3.55

[a]Prepared by Schotten–Baumann condensation.
[b]C—CH$_2$—CH$_2$—C.

TABLE 2. Yields and Characterization of Acetic Mixed Anhydrids (IVa–IVe)

Compound IV	Yield, %	mp, °C	Brutto formula (molecular weight)	Analysis, N, % Calcd.	Analysis, N, % Found	IR data, in cm^{-1} $\nu_{C=O}$	IR data, in cm^{-1} (anhydride)	IR data, in cm^{-1} $\nu_{C=O}$ (urethane)	^{1}H-NMR data, δ_{CH_3} (in ppm)
a	72	170 (dec.)	$C_{22}H_{20}N_2O_{10}$ (472.4)	5.93	6.04	1810,	1745	1720	2.33
b	83	175 (dec.)	$C_{24}H_{24}N_2O_{10}$ (500.5)	5.60	5.79	1800,	1736	1716	2.36
c	85	141	$C_{24}H_{24}N_2O_{11}$ (516.5)	5.42	5.51	1802,	1766	1726	2.55
d	80	82	$C_{26}H_{28}N_2O_{12}$ (560.5)	5.00	5.59	1804,	1744	1712	2.36
e	83	Oil	$C_{28}H_{32}N_2O_{13}$ (604.6)	4.63	—	1835,	1765	1715	2.35

TABLE 3.   Conditions and Results for the Synthesis of Poly(Urethane-Anhydride)s (Va–Ve)

Polymer V	T, °C	t, min	$\overline{M}_n$	$\overline{M}_w$ [a]	T_m, [b] °C		Analysis, N, %	
							Calcd.	Found
a	180	180	8,700[c]	—	240–50	$(C_{18}H_{14}N_2O_7)_x$ $(370.1)_x$	7.57	7.06
		120	4,300[c]	—	247–53		—	—
b	180	60	5,900[c]	—	247	$(C_{20}H_{18}N_2O_7)_x$ $(398.4)_x$	7.03	7.47
		100	9,100[c]	—	245–55		—	—
		180	13,700[c]	—	240–45		7.03	7.31
	250	40	Insoluble product					
c	180	45	2,900[d]	—	125–30	$(C_{20}H_{18}N_2O_8)_x$ $(424.4)_x$	6.60	7.76
		60	3,800[d]	—	130–35		6.60	7.15
		80	4,150[d]	—	128		6.60	7.16
		340	Insoluble product					
d	170	240	5,300[a]	26,900	148–55[e]	$(C_{22}H_{22}N_2O_9)_x$ $(459.2)_x$	6.11	6.22
e	170	240	1,090[a]	2,500	50–70	$(C_{24}H_{26}N_2O_{10})_x$ $(502.5)_x$	—	—
		360	6,200[a]	18,500	—		—	—
		480	1,400[a]	8,200	90–110[f]		5.57	4.21

[a] Determined by GPC.
[b] Determined by melting point microscopy.
[c] Determined by end-group analysis (standard deviation ± 3%).
[d] Determined osmometrically.
[e] $T_g = 96$°C (DSC).
[f] $T_g = 43$°C (DSC).

osmometry with a Knauer-type osmometer in THF solution. GPC was run in THF (flow rate 1.0 mL/min; temperature 40°C) on a Knauer-type gel chromatograph by using columns calibrated with polystyrene standards. DSC measurements were conducted on a Perkin-Elmer DSC 2B thermal analyzer at a heating rate of 10°C/min. The DTA instrument used was previously described [14]. Thermogravimetry (TG) of powdered polymer samples was performed with a thermal balance [15] at a heating range of 5 and 10°C/min in air.

RESULTS AND DISCUSSION

The synthesis of polyanhydrides (V) having urethane bonds in the main chain was based on the melt polycondensation [16] of mixed anhydrides (IV) prepared from bis(4-carboxyphenyl-amino-carbonyloxy)alkanes or oxyalkanes (III) and acetic anhydride as shown in Scheme 1. In order to obtain the required diacids (III), 4-aminobenzoic acid (ABA) (2 mol) was acylated with bis(chloroformate)s (II) (1 mol) in pyridine to give yields of 50% up to 83% with the exception of the diacid IIIe. In this case the lower yield (33%) is probably caused by side reactions which were not further studied in this work. The use of N,N-dimethylaminopyridine (DMAP) as catalyst does not increase the yields of the acylated products (III). The bis(chloroformate)s (II) were prepared from diols (I) by a simplified chloroformylation method using disphosgene or triphosgene instead of phosgene [17]. Because the products obtained could not be purified by distillation, the elemental analyses of the crude reaction products were less satisfactory. However, both IR spectra (ν_{CH_2} = 2840–3000, $\nu_{C=O}$ = 1800–1820, ν_{C-Cl} = 690–695 cm^{-1}) and the conversion into well-known carbamates by the reaction with ammonia [18] were in perfect agreement with the expected structures (IIa–IIe).

The structures assigned to the diacids (III) and acetic mixed anhydrides (IV) are supported by elemental analysis and IR and ^{1}H-NMR spectroscopy (Tables 1 and 2).

In accordance with the previously described behavior of acetic mixed anhydrides containing amide groups [6], thermogravimetric analyses indicated that polycondensation of the mixed anhydrides IVd and IVe having ether bonds in the molecule took place in the melt due to their low melting points (Fig. 1, Table 2). However, in the presence of an alkylene spacer as in the case of the mixed anhydride IVb, polycondensation occurred at 155°C owing to its elimination of acetic anhydride (Fig. 1). Therefore, the polycondensation was carried out below 180°C under vacuum. The resulting polyanhydrides Va, Vd, and Ve are soluble in DMF, DMSO and THF, respectively, and their IR spectra exhibit carbonyl bands at 1738–1778 cm^{-1}, proving the presence of anhydride groups. In contrast, at higher temperatures or on prolongation of the reaction time, insoluble products were formed in the cases of the anhydrides IVb and IVc, respectively. The results of polycondensations summarized in Table 3 also suggest that the molecular weights of the polymers formed did not increase with increasing reaction times in all cases. This is in accordance with results of the melt polycondensation of acetic mixed anhydrides from sebacic acid and bis(4-carboxyphenoxy)alkanes by Domb and Langer [19]. The polyanhydrides (V) have molecular weights up to $\overline{M}_n$ = 13,700 and $\overline{M}_w$ = 26,900 g/mol and generally no T_g values. In the case of preparation of polyanhydride Ve,

$$HO-R-OH \qquad \text{I}$$

$$\bullet Cl-CO-OCCl_3 \quad | -2\,HCl$$
$$(THF)$$

$$Cl-OC-O-R-O-CO-Cl \qquad \text{II}$$

$$+2\,HOOC-\langle\!\!\langle\text{—}\rangle\!\!\rangle-NH_2 \quad | -2\,HCl$$
$$(pyridine)$$

$$HOOC-\langle\!\!\langle\text{—}\rangle\!\!\rangle-HN-OC-O-R-O-CO-NH-\langle\!\!\langle\text{—}\rangle\!\!\rangle-COOH \qquad \text{III}$$

$$+2\,(CH_3CO)_2O \quad | -2\,CH_3COOH$$

$$CH_3-OC-O-OC-\langle\!\!\langle\text{—}\rangle\!\!\rangle-HN-OC-O-R-O-CO-NH-\langle\!\!\langle\text{—}\rangle\!\!\rangle-CO-O-CO-CH_3 \qquad \text{IV}$$

$$160-180°C \quad | -(CH_3CO)_2O$$

$$\left[OC-\langle\!\!\langle\text{—}\rangle\!\!\rangle-HN-OC-O-R-O-CO-NH-\langle\!\!\langle\text{—}\rangle\!\!\rangle-CO-O\right]_n \qquad \text{V}$$

I-V	a	b	c	d	e
R	$(CH_2)_2$	$(CH_2)_4$	$(CH_2)_2-O-(CH_2)_2$	$(CH_2-CH_2-O)_2-(CH_2)_2$	$(CH_2-CH_2-O)_3-(CH_2)_2$
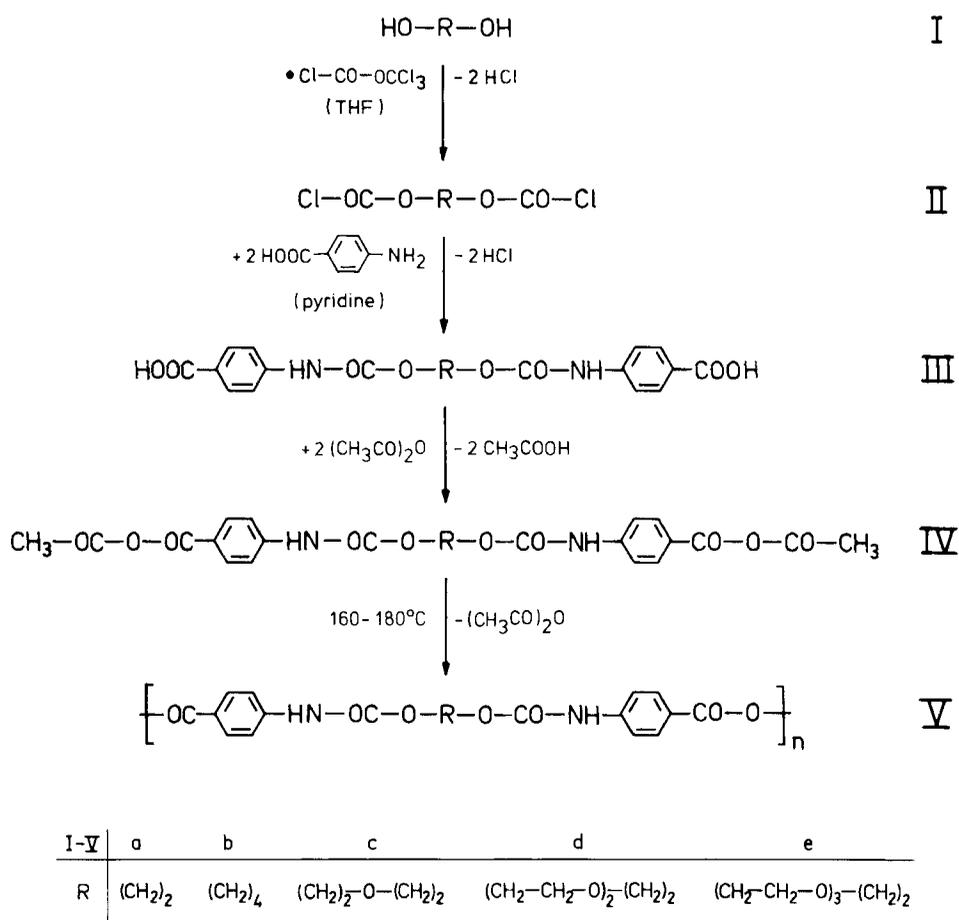
SCHEME 1. Synthesis of polyanhydrides containing urethane linkages and alkylene and oxyalkylene moieties in the main chain (Va-e)

prolongation of the reaction (480 min at 170°C) results in a product of low molecular weight with a nitrogen content lower than the calculated value. This suggested that decomposition occurred during or after polycondensation. The weight-to-average-molecular-weight ratios determined by GPC measurements of polyanhydrides Vd and Ve indicate a relatively broad molecular weight distribution which may be attributed to the formation of low molecular weight cyclic macromers during the melt polycondensations [19, 20]. The polyanhydrides Va and Vb display high melting points and are only soluble in DMF and DMSO whereas the polymers Vc-Ve containing oxyalkylene moieties exhibit high solubility in THF. In that case, the lower melting points are due to higher flexibility of oxyalkylene spacer groups in the backbone.

To study the relationship between polymer structure and hydrolytic stability, the synthesized polyanhydrides V as well as the previously described poly(amide-anhydride)s and poly(ester-anhydride)s (VI and VII) [5-7] (Scheme 2) were hydrolyzed in water at pH 7.4 and 37°C. From the data of the mass loss of thin disk-
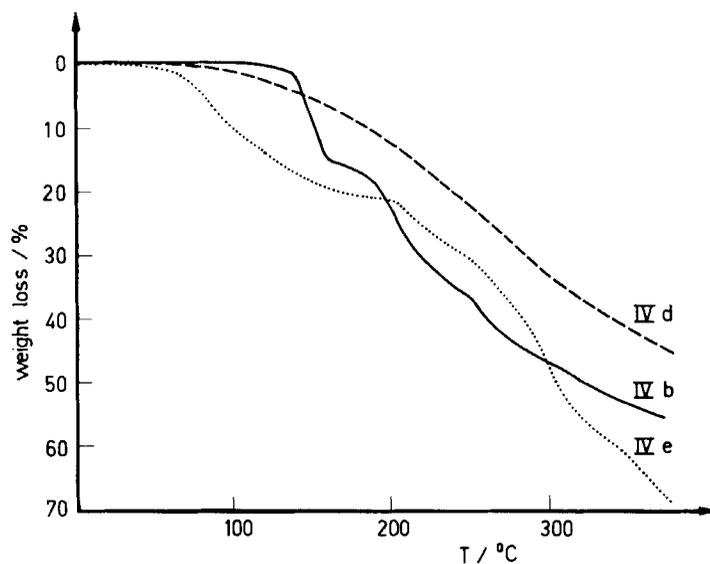
FIG. 1. Thermal gravimetric analysis of the acetic mixed anhydrides IVb, IVd, and IVe at a heating rate of 10°C/min.

shaped samples, it is evident that the rate of hydrolytic degradation of these polyanhydrides is dependent to a great extent upon both the structure and the molecular weight. With comparable molecular weights, the degradation of samples of the polyanhydrides Ve, VIb, and VIIb containing the same oxalkylene unit occurred faster than that of the corresponding polymers Vb, VIa, and VIIa having alkylene spacer groups in the backbone. On the other hand, the nature of linkage (urethane, ester, amide) of the spacer group in the main chain did not influence the degradation rate regularly. However, it must be noted that hydrolytic degradation of these polymers under heterogeneous conditions may also be influenced to a great extent by the crystallinity of the polymers. The morphological characterization of synthesized polyanhydrides is under investigation.

VI , VII	R		X
a	$(CH_2)_4$	VI	NH
b	$(CH_2-CH_2-O)_3(CH_2)_2$	VII	O
c	$(CH_2-CH_2-O)_2(CH_2)_2$		
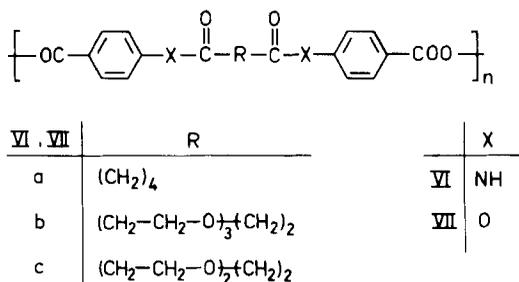
SCHEME 2. Structure of poly(amide-anhydride)s VIa-c and poly(ester-anhydride)s VIIa-c containing alkylene and oxyalkylene moieties in the backbone [5-7].
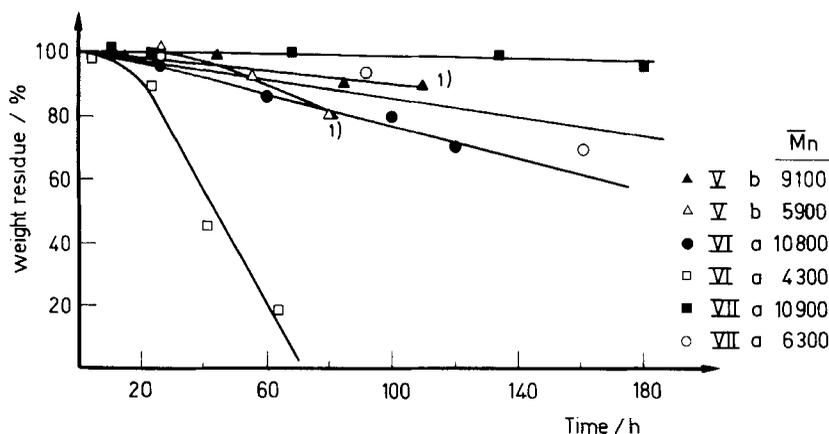
FIG. 2. Hydrolytic degradation of poly(urethane-anhydride) Vb, poly(amide-anhydride) VIa, and poly(ester-anhydride) VIIa having tetramethylene units in the backbone at pH 7.4 and 37°C. 1): Simple tablet which decomposes during hydrolysis; compression molding of the sample was not possible.

Apart from a small delay at the beginning of hydrolysis, polyanhydrides V, VI, and VII display a nearly zero-order surface degradation (Figs. 2 and 3). The rate constants determined from the straight part of the curves are given in Table 4.

As shown in Table 5, the degradation rate of polyanhydride VIc increases with increasing pH of the hydrolysis medium due to the accelerated hydrolysis rate of the anhydride groups. In addition, salt formation of the resulting monomeric dicarboxylic acids leads to their faster removal from the matrix surface. Furthermore, the increase in temperature of the hydrolysis mixture results in an increased degradation rate.
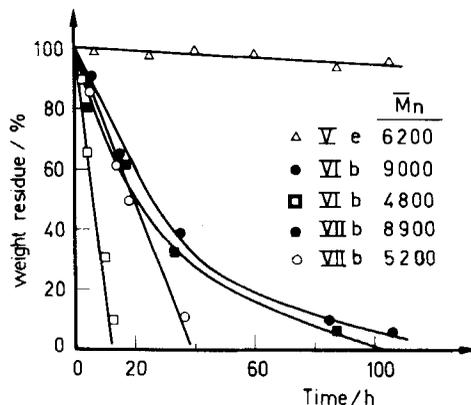
FIG. 3. Hydrolytic degradation of poly(urethane-anhydride) Ve, poly(amide-anhydride) VIb, and poly(ester-anhydride) VIIb having trioxatridecane moieties at pH 7.4 and 37°C.

TABLE 4. Rate Constants k of the Hydrolytic
Degradation of Poly(Urethane-Anhydride) Vb,
Poly(Amide-Anhydride) VIa, and Poly(Ester-Anhydride)s
(VIIa and VIIb) (pH 7.4; 37°C)

Polymer	$\overline{M}_n$, g/mol	k,[a] mg/h·cm^2
Vb	5,900	0.35
	9,100	0.15
	13,700	0.09
VIa	6,800	0.38
	10,800	0.22
VIIa	6,390	0.12
	10,900	0.02
VIIb	5,900	0.71
	10,000	0.44

[a]$k = m/At$, where m = mass loss of polymers at the time t,
t = time of hydrolysis, A = area of the polymer matrix, and k =
rate constant.

Under these conditions, degradation of the polyanhydrides proceeds with
cleavage of the anhydride bonds as confirmed by the IR and UV spectra of the
dicarboxylic acids III isolated from the hydrolysis solution. Hydrolysis of urethane
bonds in polymers V and of amide linkages in polymers VI was not observed at pH
7.4 and 37°C. However, the hydrolytic degradation of polyanhydride VIIb ($\overline{M}_n$ =

TABLE 5. Dependence of Rate Constants k of the
Hydrolytic Degradation of Poly(Amide-Anhydride)
VIc on the pH and the Temperature

pH	T, °C	k,[a] mg/h·cm^2
3.0	30	1.0
5.0	30	1.3
7.4	30	2.0
9.0	30	60.0
7.4	10	0.4
7.4	20	0.7
7.4	40	4.7
7.4	50	8.7

[a]Cf. Table 4.
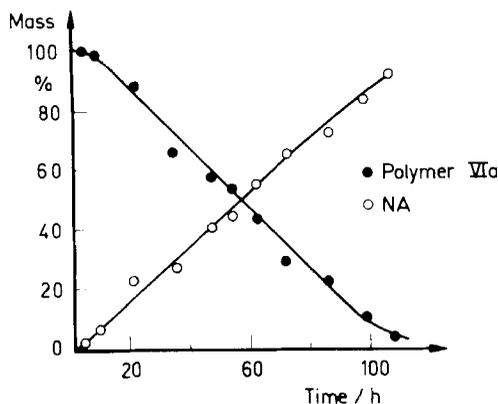
FIG. 4. 4-Nitroanisole (NA) release and hydrolytic degradation of poly(amide-anhydride) VIa ($\overline{M}_n$ 6800) at pH 7.4 and 37°C.

5200) gives rise to the formation of 4-hydroxybenzoic acid and 4,7,10-trioxatridecane diacid in the mole ratio 2:1, indicating cleavage of both the anhydride and ester bonds in the backbone.

The release properties of the synthesized polyanhydrides were examined by the release of 4-nitroanisole (NA) as a model drug from compression molded disks of polymer VIa ($\overline{M}_n$ = 6800). The profile shown in Fig. 4 is also representative for other polyanhydride/NA combinations prepared. The release of NA, which was determined by its UV spectrum, followed polymer degradation after a short delay at the beginning of hydrolysis. Such a delay has been observed with a somewhat longer length of time in the case of polymers V which have urethane bonds in the backbone. By admixture of NA, only a small delay in the degradation of the polymer matrix took place.

CONCLUSIONS

The introduction of urethane linkages into the main chain of polyanhydrides was achieved by polycondensation of bis(4-carboxyphenyl-aminocarbonyloxy) alkanes and oxyalkanes, respectively, based on 4-aminobenzoic acid. Because of the presence of alkylene or oxyalkylene units in the backbone, varying melting points and solubilities of these novel polyanhydrides could be obtained. Like the poly(amide anhydride) analogs, the urethane linkages in the chain of the synthesized polymers remain intact throughout hydrolysis under the conditions studied. In contrast, poly(ester-anhydride)s were degraded by cleavage of both the anhydride and the ester bonds. The poly(urethane-anhydride)s displayed nearly constant degradation rates and model drug release rates under hydrolytic conditions. This demonstrates the potential suitability of these polymers for use as biodegradable carriers in drug delivery systems.

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