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Synthesis of Polyanhydrides: Melt-Polycondensation, Dehydrochlorination, and Dehydrative Coupling

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ABSTRACT: Synthesis of polyanhydrides was studied by melt-polycondensation, dehydrochlorination, and dehydrative coupling. Melt-polycondensation produced the highest molecular weight and did not require an isolation step. Estimated weight-average molecular weights of over 50 000 could be obtained by extended polymerizations of over 24 h. For polymers that are thermally unstable or high-melting, the polymerization could be achieved at room temperature by reacting acyl chlorides with carboxylic acids in solution. Among the six solvent systems studied, the nonaqueous interfacial hexane–dimethylformamide solvent pair yielded the highest molecular weight. A new approach of forming polyanhydride via dehydrative coupling of the carboxyl groups was also demonstrated. Among the seven dehydrative coupling agents studied, bis[2-oxo-3-oxazolidinyl]phosphinic chloride and phenyl *N*-phenylphosphoroamidochloridate were the most effective. The degree of polymerization obtained for the dehydrochlorination and dehydrative coupling under optimal conditions was from 15 to 30.

Introduction

Synthesis of polyanhydrides was first reported by Bucher and Slade in 1909.[1] In the 1930s Carothers and Hill prepared a series of aliphatic polyanhydrides intended as substitutes for polyesters in textile applications.[2,3] Conix in the late 1950s studied the poly[bis(*p*-carboxyphenoxy)alkane anhydrides] and reported much improved hydrolytic resistance as well as excellent film- and fiber-forming properties for these aromatic polyanhydrides.[4,5] Yoda subsequently studied a number of aromatic and heterocyclic polyanhydrides.[6–11] Including copolymers, over 100 polyanhydrides had been prepared by 1965.[12] However, these polyanhydrides were never commercialized, presumably due to the problem of hydrolytic instability. Little research has been done on polyanhydrides in the past two decades.

Our interest in polyanhydrides stems from our involvement in biomaterials and controlled drug delivery research.[13–15] Polyanhydride synthesis has always been centered around thermal coupling involving mixed-anhydride prepolymers. Data on physical characterization, in particular the molecular weight properties, have been scarce. The fact that the polyanhydride chemistry has only been studied sparingly and that anhydrides can be obtained via many different synthetic pathways prompted us to examine the existing methods as well as to explore new methods of synthesis.

The formation of an anhydride is essentially a dehydrative coupling of two carboxyl groups. To facilitate condensation, Carothers and Hill first formed a prepolymer by converting the carboxyl group to a mixed anhydride with acetic acid before subjecting the prepolymer to melt-polycondensation (eq 1). However, this method

$$\mathrm{HOOC{-}R{-}COOH} \xrightarrow{\mathrm{(CH_3CO)_2O}} \mathrm{H_3CC(O){-}O{-}C(O){-}R{-}C(O){-}O{-}C(O)CH_3} + \mathrm{CH_3COOH} \xrightarrow[\text{vacuum}]{\Delta} \mathrm{{-}(R{-}C(O){-}O{-}C(O)){-}} + \mathrm{(CH_3CO)_2O} \quad (1)$$

suffers from certain limitations: the reversible thermal depolymerization may limit the highest molecular weight obtainable, and the acetic anhydride reflux may be unsuitable for many heat-sensitive monomers. Milder reaction conditions are therefore desirable.

Polyanhydride formation can be effected at room temperature by a dehydrochlorination between a diacid chloride and a dicarboxylic acid (eq 2). It is essentially

$$\mathrm{HOOC{-}R{-}COOH} + \mathrm{ClOC{-}R'{-}COCl} \xrightarrow{\text{base}} \mathrm{{-}(R{-}C(O){-}O{-}C(O){-}R'{-}C(O){-}O{-}C(O)){-}} + \text{base}\cdot\mathrm{HCl} \quad (2)$$

a Schotten–Baumann condensation, a reaction extensively studied for polyamide, polyester, and polycarbonate synthesis. However, only Yoda et al.[6] and Windholz[16] have used this reaction for obtaining polyanhydrides. Since the carboxylic hydrogen is less reactive than that of an amine, alcohol, or mercaptan, the condensation is expected to be

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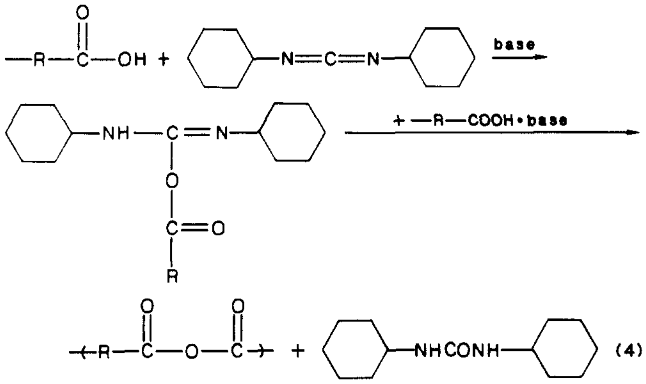
less efficient. Nevertheless it was hoped that under optimal conditions the reaction may still be able to yield useful polyanhydrides.

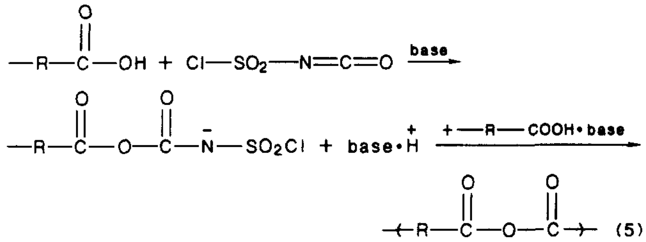
In searching for an alternative synthetic route, we also considered approaches where sensitive monomers do not have to be subjected to the acylation conversion. We thus looked for powerful dehydrative coupling reagents that function in mild reaction conditions. One class of reagents that appears particularly promising is the organophosphorus compounds. In peptide synthesis, the hypothesis is that the organophosphorus compound first forms a reactive mixed-anhydride intermediate with the carboxylic acid.[17] The peptide bond is formed upon the nucleophilic attack of an amino group. If instead of an amino group a second carboxyl group is allowed to react with the intermediate, a carboxylic anhydride is formed. The reaction has been utilized by Cabre-Castellvi[18] and Mestres[19] in obtaining monomeric anhydrides. Hence with a dicarboxylic acid, polyanhydride formation seems feasible according to the proposed reaction mechanism[18] (eq 3).

$$\mathrm{ClP(O)R_2} + \mathrm{-R'-COOH} \xrightarrow{\text{base}}$$
$$\mathrm{-R-C(O)-O-P(O)R_2} + \text{base}\cdot\mathrm{HCl} \xrightarrow{+\,\mathrm{-R'-COOH}\cdot\text{base}}$$
$$\mathrm{-(R'-C(O)-O-C(O))-} + \text{base}\cdot\mathrm{HOP(O)R_2} \quad (3)$$

In principle, other types of dehydrative agents may also effect polyanhydride formation[20,21] (eq 4 and 5).



(4)


$$\mathrm{-R-\overset{O}{\overset{\|}{C}}-OH} + \mathrm{Cl-SO_2-N{=}C{=}O} \xrightarrow{\text{base}} \mathrm{-R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-\overset{-}{N}-SO_2Cl} + \text{base}\cdot\overset{+}{\mathrm{H}} \xrightarrow{+\mathrm{-R-COOH}\cdot\text{base}} \mathrm{-\!\!\!+R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}+\!\!\!-} \quad (5)$$

In this study, we examined all three routes of polyanhydride synthesis: melt-polycondensation, dehydrochlorination, and dehydrative coupling. The polymerization kinetics in the melt-polycondensation was studied qualitatively and the physical properties of the polymers were characterized. The dehydrochlorination polymerization was studied separately in solution, in aqueous interfacial systems, and in nonaqueous interfacial systems. The focus of the dehydrative coupling reaction was in the use of organophosphorus catalysts. In both the Schotten–Baumann and the dehydrative coupling reactions, the effects of solvents, bases, monomer reactivity, reaction conditions, and workup procedures were investigated.

Experimental Section

Synthesis. Bis(*p*-carboxyphenoxy)alkanes for the melt-polycondensation were synthesized according to the method described by Conix.[22] 2,2'-(p-Xylylenedithio)diacetic acid was synthesized as described by Yoda.[10] Sebacic acid and 1,4-phenylenedipropionic acid were obtained from Aldrich Chemical Co. Sebacic acid was recrystallized twice in methanol, and 1,4-phenylene dipropionic acid once in acetone before use. The diacids were reacted with excess acetic anhydride (approximately 50 g in 500 mL) in a fractional distillation setup. A 30-cm-long Vigreux column was used and the distillation rate was adjusted to 100 mL/h. The reflux lasted between 1 and 2 h, with occasional replenishment of fresh acetic anhydride. The rest of the solvent was evaporated in a rotary vacuum evaporator at 70 °C, and the residue was recrystallized in a mixed solvent of chloroform and petroleum ether (20:80 (v/v)). The condensation of the prepolymer thus obtained was carried out in an evaporator initially purged with nitrogen at a pressure of 10^{-4} mmHg and at various temperatures: 100–130 °C for polymers **1**, **5**, **7**, and **8**, 160 °C for polymers **4** and **6**, 200 °C for polymer **2**, and 280 °C for polymer **3** (Table I). The polymers were purified by reprecipitation in petroleum ether.

The diacids used in the dehydrochlorination were recrystallized in methanol. Terephthaloyl chloride, 2,6-pyridine diacid chloride, and isophthaloyl chloride were recrystallized in petroleum ether. These acid chlorides were freshly recrystallized before every reaction. Fumaryl chloride was vacuum-distilled at 40 mmHg. Glutaryl chloride and sebacoyl chloride were used as received. The solvents were dried over molecular sieves (Type 4A) and all glassware was oven-dried. For a typical solution polymerization, 20 mmol of the diacids and 40 mmol of base were dissolved in 20 mL of solvent (e.g., dichloromethane or chloroform). To the magnetically stirred mixture was added 20 mmol of the acyl chloride in 200 mL of the above solvent in a single portion. The reaction flask was stoppered by a moisture guard tube containing calcium chloride. After 2 h of reaction at room temperature, the mixture was quenched in 1 L of petroleum ether under agitation. This would also trap the triethylamine hydrochloride salt. For this reason the yield was only estimated. The polymers can be cleaned by shaking the reaction mixture in 50 mL of cold methanol before quenching. However, that would slightly degrade the polymer as evidenced by IR spectroscopy.

For the dehydrative coupling reactions, the diacid monomers were purified as described above. The coupling agent bis[2-oxo-3-oxazolidinyl]phosphinic chloride was synthesized as described by Cabre-Castellvi[18] and diethyl phosphorobromidate by the method of Gorecka.[23] The other coupling agents were used as received. In a typical reaction, the diacid (10 mmol in 25 mL of solvent) dissolved in the presence of acid acceptor (20 mmol) was added in a single portion to a magnetically stirred solution containing the coupling agent (5 mmol in 5 mL of solvent). The reaction was conducted at room temperature in a stoppered flask. Solvents and glassware were as described above. The following workup procedures were used: W1, the resulting suspension was filtered, the solid was washed with 50 mL of chloroform, and the filtrate was vacuum-evaporated; W2, the reaction mixture was directly quenched into petroleum ether; W3, the reaction mixture was extracted with 25 mL of cold dilute HCl, and the organic phase was then quenched into petroleum ether.

Characterization. The IR spectra were obtained from a Perkin-Elmer spectrophotometer Model 1430 on samples either film cast in chloroform onto NaCl plates or pressed into KBr pellets. The thermal properties of the polymers were determined on a Perkin-Elmer DSC-4 calorimeter. The previous thermal history of the samples was erased in a preliminary heating cycle, and the transition temperatures were determined at a heating rate of 20 °C/min. The molecular weight properties were characterized by gel permeation chromatography (GPC), vapor pressure osmometry (VPO), and intrinsic viscosity. The GPC was run in a chromatography system consisting of the Perkin-Elmer Series 10 pump, the LC-25 RI detector, the 3600 data station, and an LKB 2140 spectral detector. Samples were analyzed in chloroform by using two PL Gel columns connected in series (Polymer Laboratories; 100- and 1000-Å pore sizes). Polystyrene (Polysciences) was used as the calibration standard. The VPO determinations were done in a Type 11.00 Knauer osmometer equipped with a Type 06.00 digital meter. Samples were measured in chloroform at 45 °C. The M_n values obtained from VPO were typically 30–50% below that from GPC. The lower values are expected in view of the presence of oligomers. On the basis of this comparison, polystyrene was regarded as an

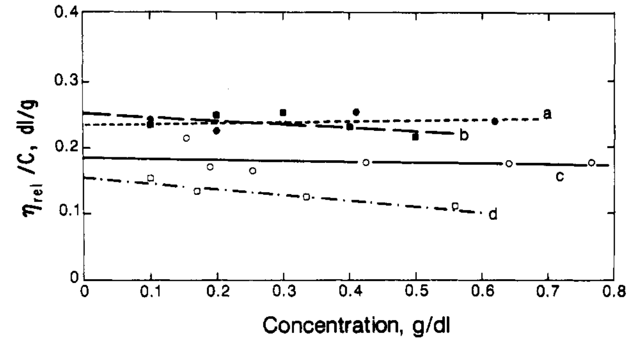


Figure 1. Intrinsic viscosity of melt-polycondensed polyanhydrides determined in chloroform at 30 °C. Curves a–d correspond to polymers **5**, **6**, **7**, and **1** in Table I.

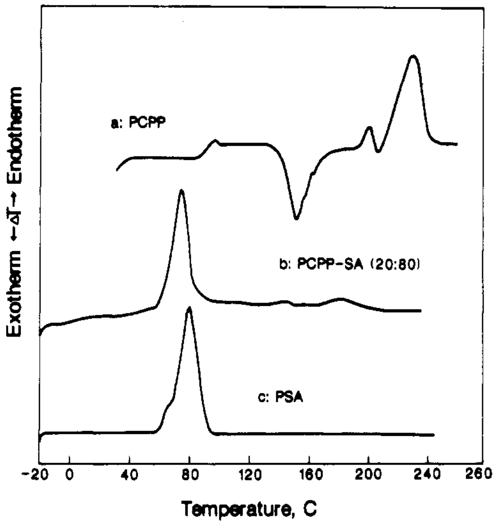


Figure 2. DSC scans of polyanhydrides at a rate of 20 K/min. Curves a–c correspond to polymers **3**, **5**, and **1** in Table I.

adequate standard for the GPC determination. The intrinsic viscosity was measured in chloroform at 30 °C using a Ubbelohde viscometer. Hydrolysis of the polymers was conducted under in vitro conditions, in pH 7.4 0.1 M phosphate buffer at 37 °C. The degradation kinetics was followed by measuring the UV absorbance of the periodically changed buffer solutions in the Perkin-Elmer UV spectrophotometer 553. The hydrolysis rates were estimated by computing the slope of the linear portion in the degradation profile.[14] Alternatively, the weight change of samples in buffer was measured as a function of time. Samples were disk-shaped with diameters ranging from 5 to 15 mm.

Results

Melt-Polycondensation. The physical properties of representative melt-polycondensed polyanhydrides are summarized in Table I. Representative viscosity and DSC plots are shown in Figures 1 and 2, respectively. These polymers share several common features. They all possessed fiber-forming properties in the molten state. Except for poly[2,2′-(*p*-xylylenedithio)diacetic anhydride], these polymers showed a distinct melting transition. On exposure to atmosphere, the polymers hydrolyzed gradually, changed from pliable to brittle, and became less soluble in good solvents such as chloroform and methylene chloride. The hydrolysis was evidenced by the emergence of carboxylic OH and carbonyl bands in the IR spectra. The findings here closely resembled those reported by Carothers and Hill,[3] Yoda,[10] and Conix.[5] The hydrolytic resistance of the polymers was highly dependent on the chemical structure of the backbone. The degradation rates varied over 3 orders of magnitude for chemical backbones ranging from 2,2′-(*p*-xylylenedithio)diacetic acid to 1,6-bis(*p*-carboxyphenoxy)hexane (Table I).

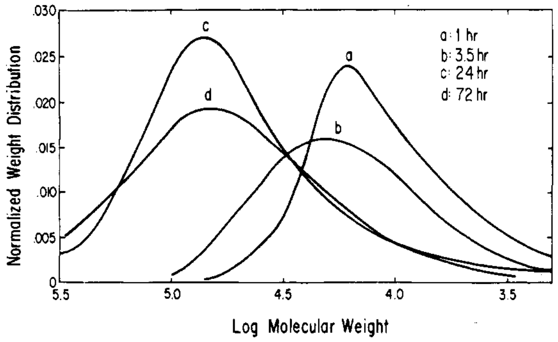


Figure 3. Kinetics of the melt-polycondensation of the copolyanhydride of bis(*p*-carboxyphenoxy)propane and sebacic acid (20:80 wt %) (**5**) at 10^{-4} mmHg and 120 °C. Molecular weight distributions obtained at different polymerization times are shown: (a) 1 h; (b) 3.5 h; (c) 24 h; (d) 72 h.

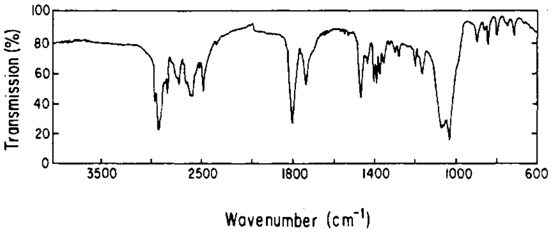
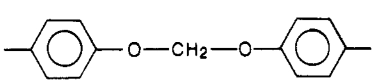
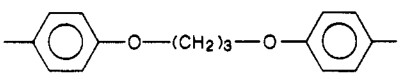
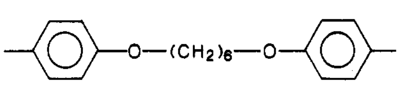
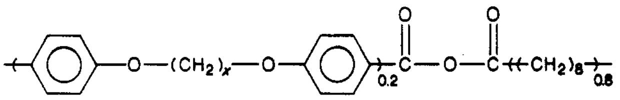
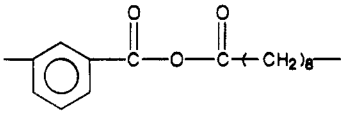
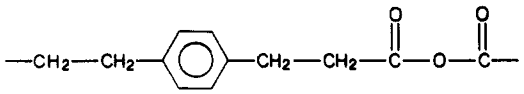
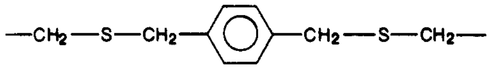


Figure 4. IR spectrum of poly(sebacic anhydride) (**1**) obtained by the Schotten–Baumann condensation of sebacoyl chloride and sebacic acid in a nonaqueous interfacial system of hexane and dimethylformamide.

The condensation commenced readily under low pressure and continued for the first 2–3 h. Condensation was hardly noticeable after this period when the amount of distillate collected was negligible. Prolonged vacuum distillation, however, improved the molecular weight. Figure 3 shows the increase in molecular weight of the copolymer poly[bis(*p*-carboxylphenoxy)propane sebacic acid anhydride] (PCPP–SA) with time. Nevertheless it is crucial to monitor the reaction temperature to prevent decarboxylation or decarbonylation. In this study, these side reactions appeared to be insignificant at polymerization temperatures below 130 °C. When the PCPP–SA polymerization was run at 175 °C and 10^{-4} mmHg for 4 days, a tarry product that swelled extensively in chloroform was obtained. The soluble portions had an estimated weight-average molecular weight of 52 800 but also a polydispersity value of >10. This result suggests significant depolymerization occurring on extensive heating. The IR analysis revealed that there was more than one type of anhydride bond present, indicating the presence of cross-linking and cyclic oligomers.

Schotten–Baumann Condensation. Results of representative trials are shown in Table II. IR spectroscopy provides a convenient means of appraising the effectiveness of the condensation reaction. Since the anhydride formation would shift the carbonyl stretch to a higher frequency, from 1700 to 1720–1810 cm^{-1}, it is possible to estimate the success of the polymerization by monitoring the monomeric carbonyl and carboxylic OH stretches. For instance, the IR spectrum of the product from reaction no. 14 (Table II) is indicative of an effective condensation (Figure 4). None of the peaks belonging to the monomers—the broad carboxylic OH peak around 3000 cm^{-1}, the acid chloride carbonyl stretch at 1785 cm^{-1}, the acid carbonyl stretch at 1695 cm^{-1}, and the carbon–chlorine stretch at 975 cm^{-1}—appeared in the spectrum. The relative intensities of the anhydride doublet would also reveal the nature of the anhydride bond. A linear anhydride would yield a more intense vibration at the higher

Table I
Physical Properties of Melt-Polycondensed Polyanhydrides

polymer	chemical structure of backbones	thermal properties T_g, °C	thermal properties T_m, °C	mol wt $M_n \times 10^{-3}$	mol wt $M_w \times 10^{-3}$	$[\eta]^{30°C}_{CHCl_3}$, dL/g	hydrolytic degrad rate, μg cm^{-2} h^{-1}	remarks
1	$-(CH_2)_8-$	*a*	78	4.11	23.9	0.16	210	polymerized for 12 h; becomes brittle on exposure to atmosphere
2		86	196	5.42	11.8		180	
3		92	230	6.00	15.0		1.4	highly crystalline; has a distinct exotherm at 150 °C; flexural strength = 400 psi; Young's modulus = 186 000 psi
4		*b*	123	5.28	9.53		0.2	
5		*b*	74	4.3	52.8	0.24	160	polymerized for 96 h
6		*b*	145	6.61	22.6	0.25	140	an elastic and sticky material when precipitated in petroleum ether from chloroform
7		*a*	113	7.88	38.2	0.18		polymerized for 48 h; M_n = 4800 by VPO
8		*a*	116	3.60	7.92		320	takes several days to recrystallize from melt

[a] Glass transition not detected above room temperature. [b] Glass transition not detected above −20 °C.

frequency, while the reverse would be true for cyclic anhydrides.[24]

For the solution polymerization, solvents such as dichloromethane, chloroform, benzene, and ethyl ether yielded comparable results in terms of molecular weights and yields. Polymerization took place on contact of the monomers and was essentially complete within 1 h as monitored by GPC. The degree of polymerization was in the range of 20–30. However, lower molecular weight products were obtained for less reactive monomers such as isophthaloyl chloride (reaction no. 17, Table II). For glutaryl chloride and the unsaturated fumaryl chloride (reaction no. 8 and 9), extensive side reactions apparently prevented the polymer formation.

The mode of reactant introduction affected the degree of polymerization. Adding the acid solution dropwise to the acid chloride solution consistently produced superior results in terms of yield and molecular weight as compared

Table II
Synthesis of Polyanhydrides by Schotten–Baumann Condensation

reacn no.	monomers	solvent system	reacn conditions	IR observations	comments
1	adipic acid + terephthaloyl chloride (TC)	solution, dichloromethane	0.1 M/TEA/2 h	anhydride peaks at 1805 (s) 1725 (m), 1045 (s), and 995 (m) cm^{-1}, no evidence of carboxylic OH	good yield; violent gas evolution on contact of monomers; rapid solid formation
2	sebacic acid (SA) + TC	solution, chloroform	0.1 M/TEA + 10% excess pyridine/2 h	1805 (s), 1735 (m), and 1050 (s) cm^{-1}, carboxylic OH	same as 1; M_n = 3980 by GPC
3	1,12-dodecanedioic acid + TC	solution, dichloromethane	0.2 M/TEA/2 h	1800 (s), 1725 (m), 1050 (s), and cm^{-1}, no carboxylic OH	same as 1; M_n = 5200 by GPC
4	terephthalic acid + TC	solution, chloroform	0.2 M/TEA/3 h	1805 (s), 1725 (m), and 1045 (s), no carboxylic OH	good yield; some gas evolution; gradual solid formation during the course of reaction; condensation product $N(C_2H_5)_3{\cdot}HCl$ confirmed by IR and melting point analysis
5	SA + 2,6-pyridine diacid chloride (PC)	solution, chloroform	0.2 M/TEA + 10% excess pyridine/2 h	1810 (s), 1740 (m), and 1040 (s) cm^{-1}, no carboxylic OH	same as 1
6	SA + PC	solution, benzene and ethyl ether	0.2 M/TEA/2 h	same as 5	similar to 1% solution becoming more viscous as reaction progressed
7	SA + isophthaloyl chloride	solution, chloroform	0.2 μ/TEA/2 h	1805 (s), 1785 (m), 1730 (m), 1695 (w), and 1045 (m) cm^{-1}	moderate yield; slight gas evolution; M_n = 2200 by GPC
8	SA + fumaryl chloride	solution, dichloromethane	0.2 M/TEA/2 h	evidence of cyclic anhydrides, with peaks at 1810 (m) and 1730 (s) cm^{-1}	poor yield; solution turned black rapidly
9	glutaric acid + glutaryl chloride	solution, dichloromethane	0.2 M/TEA/2 h	no anhydride peaks, a broad intense band at 1755 cm^{-1}	poor yield; solution turned green
10	SA + TC	aqueous interfacial, water + dichloromethane	0.2 M SA in H_2O and 0.1 M TC in $MeCl_2$/NaOH/15 min	doublet at 1805 (s) and 1785 (s), 1725 (m), and 1695 (m) cm^{-1} and carboxylic OH around 3000 cm^{-1}	moderate yield; some gas evolution; pH of aqueous phase neutralized within 30 s; brittle film formation in the interface
11	SA + TC	aqueous interfacial, water + chloroform	0.5 M SA in H_2O and 0.1 M TC in $CHCl_3$/NaOH/5 min	1805 (s), 1725 (m), 1695 (w), and 1050 (s) cm^{-1}, slight evidence of carboxylic OH	same as 10
12	SA + TC	nonaqueous interfacial, hexane + dimethylformamide	0.2 M of SA in DMF and 0.2 M TC in hexane/TEA/2 h	same as 2	good yield; violent gas evolution; rapid film formation in the interface; best system for this coupling reaction
13	SA + sebacoyl chloride	same as 12	0.2 M SA in DMF and 0.2 M TC in hexane/TEA/12 h	1810 (s), 1745 (m), and 1045 (s) cm^{-1}	similar to 12; $[\eta]$ = 0.14 dL/g in $CHCl_3$; M_n = 4200 by GPC
14	SA + TC	nonaqueous interfacial, carbon tetrachloride + 1,4-dicyanobutane	0.2 M SA in DCB and 0.2 M TC in hexane/TEA/12 h	same as 2	good yield; violent gas evolution; initial film formation in the interface; solid gradually dissolved in 1,4-dicyanobutane, rendering product recovery difficult
15	SA + PC	same as 14	same as 14	same as 5	same as 14

to the reverse order of addition. This could be understood in terms of recent findings that terephthaloyl chloride complexes with triethylamine to form an ionic salt.[25] Since a slight excess of acid acceptors was often used to solubilize the acid monomers, part of the terephthaloyl chloride would be lost due to complexation. The unbalanced stoichiometry therefore accounted for the inefficient polymerization. Adding the acyl chloride in a single portion, however, yielded satisfactory results, which suggests the rate of dehydrochlorination was comparable to the rate of acid chloride–amine complexation.

Polymerizations conducted in aqueous interfacial systems undoubtedly suffered from hydrolytic decomposition. A shorter reaction time actually yielded higher molecular weight (reaction no. 10 and 11). The IR spectra showed the presence of carboxyl groups in addition to the anhydride bonds (Figure 5). In avoiding contact with water the decomposition problem was alleviated. In a nona-

Table III
Synthesis of Polyanhydrides by Dehydrative Coupling[a]

reacn no.	coupling agent	monomers	reacn and workup conditions	M_n	IR observation
1	A	sebacic acid (SA)	0.2 M/MeCl$_2$/TEA/15 min/W1	3600	anhydride doublet at 1810 (s) and cm^{-1}; 1730 (m) cm^{-1}; broad 1050 (s) cm^{-1} peak; no evidence of carboxylic OH stretch around 3000 cm^{-1}
2	A	SA	0.2 M/MeCl$_2$/pyridine/15 min/W1	3400	same as 1
3	A	SA	0.4 M/THF/TEA/15 min/W1	2600	anhydride doublet at 1810 (s) and 1725 (m) cm^{-1}; peaks at 1695 (vw) and 1050 (s) cm^{-1}; weak carboxylic OH stretch
4	A	1,4-phenylenedipropionic acid	0.2 M/MeCl$_2$/TEA/30 min/W1	3400	peaks at 1810 (s), 1740 (m), 1705 (vw), 1050 (s), and 1030 (m) cm^{-1}; no carboxylic OH
5	B	SA	0.2 M/MeCl$_2$/TEA/30 min/W2	3600	same as 1
6	B	1,4-phenylenedipropionic acid	0.2 M/CHCl$_3$/TEA/30 min/W3	3400	peaks at 1810 (s), 1745 (m), and 1050 (s) cm^{-1}
7	C	SA	0.2 M/MeCl$_2$/TEA/15 min/W2	2100	as described in 1, with a weak broad peak around 3000 cm^{-1}
8	C	1,3,5-benzenetricarboxylic acid + SA, 1:3 by moles	0.2 M/CHCl$_3$/TEA/10 days/W2	cross-linked gel	peaks at 1810 (s), 1735 (s), and 1050 (s) cm^{-1}; no evidence of carboxylic OH
9	C	1,12-dodecane	0.2 M/MeCl$_2$/TEA/30 min/W2	1200	peaks at 1815 (w), 1720 (w), 1695 (m), and 1050 (m) cm^{-1}; broad COOH stretch

[a] A = bis[2-oxo-3-oxazolidinyl]phosphinic chloride, B = phenyl *N*-phenylphosphoroamidochloridate, and C = diphenyl chlorophosphate; W1, W2, and W3 are workup procedures described in the Experimental Section. The molecular weight was estimated by GPC.

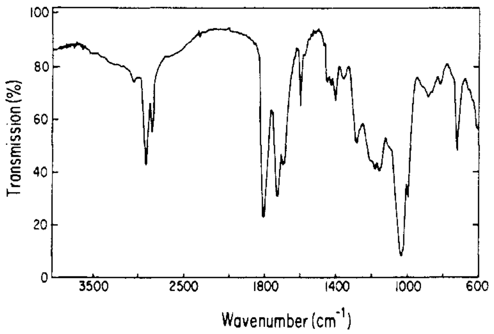


Figure 5. IR spectrum of poly(terephthalic sebacic anhydride) (**6**) obtained by an interfacial polymerization in water–chloroform and with NaOH as the acid acceptor.

queous interfacial scheme, products were obtained in close to quantitative yields and with number-average molecular weights in the range of 4000–5000. Nevertheless the choices of immiscible organic pairs are limited. Dimethylformamide (DMF) and 1,4-dicyanobutane were found to be suitable polar solvents. Between the two solvents DMF was preferred because of the ease of workup. In the carbon tetrachloride–1,4-dicyanobutane system, product recovery was difficult, as the majority of the polymer dissolved in the dicyanobutane phase. Hexane–DMF hence represents the best solvent system studied for this coupling reaction.

Dehydrative Coupling. A number of dehydrative agents were effective in coupling the carboxyl groups, although mostly oligomers were formed. IR analysis was again used to assess the efficacy of the coupling agents. The results of successful trials are summarized in Table III.

Bis[2-oxo-3-oxazolidinyl]phosphinic chloride (A) and phenyl *N*-phenylphosphoroamidochloridate (B) were the most effective coupling agents in yielding higher molecular weights. It is essential that A, as a heterogeneous catalyst, be ground into fine particles before use. When not pulverized, the agent yielded only oligomeric products. The catalyst should also be freshly prepared; even storage in sealed vials at −20 °C would impair the coupling activity. Diphenyl chlorophosphate (C) was stable to air exposure, but its coupling activity was lower than that of A and B. Diethyl phosphorobromidate was also difficult to purify; traces of bromine remaining in the compound would discolor the final polymeric products. Other coupling or dehydrative agents including dicyclohexylcarbodiimide, chlorosulfonyl isocyanate, and 1,4-phenylene diisocyanate formed only oligomers.

In general, higher molecular weights were obtained with polar solvents such as dichloromethane and chloroform. However, hygroscopic solvents such as tetrahydrofuran, acetonitrile, and dimethyl sulfoxide tended to decompose the polymer. Triethylamine, pyridine, and 2,6-lutidine were all capable acid acceptors, while 4-(dimethylamino)pyridine was ineffective.

It was difficult to isolate and purify the final products without evoking hydrolytic decomposition. Quenching the reaction mixture in a nonsolvent such as petroleum ether would trap the hydroxylated catalysts and the triethylamine hydrogen chloride salt. Washing the reaction mixture with methanol or cold dilute hydrochloric acid would effectively clean the polymer, but at the same time would induce degradation. This was clearly observed in the IR analysis in which carboxylic OH and acidic carbonyl bands emerged. The use of liquid organophosphorus agents such as B and C facilitated the workup procedure in this regard.

With a tricarboxylic acid, a cross-linked polyanhydride was produced. The product described in reaction no. 8 (Table III) was an opaque gel having no solubility in chloroform or methylene chloride. It swelled slightly in chloroform but slowly decomposed in the solvent, presumably due to traces of water in the solvent. The gel, with the high anhydride linkage density, hydrolyzed readily in pH 7.4 phosphate buffer. The hydrolysis rate was comparable to that of the relatively hydrophilic poly(sebacic anhydride).

Trends observed in the solution polymerization regarding ring formation recurred in this catalyzed reaction. Glutaric acid, α-ketoglutaric acid, and succinic acid all

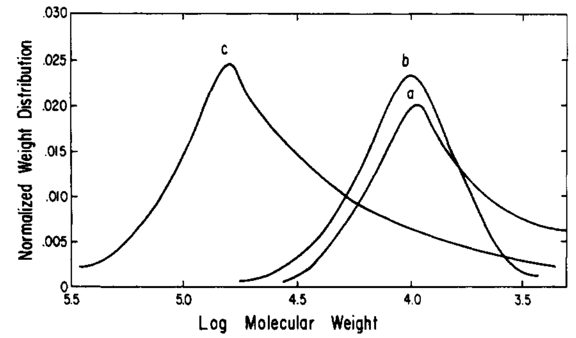


Figure 6. Comparison of the molecular weight of poly(sebacic anhydride) (1) obtained by different polymerization methods: (a) dehydrative coupling by bis[2-oxo-3-oxazolidinyl]phosphinic chloride in dichloromethane; (b) dehydrochlorination in hexane–dimethylformamide; (c) melt-polycondensation.

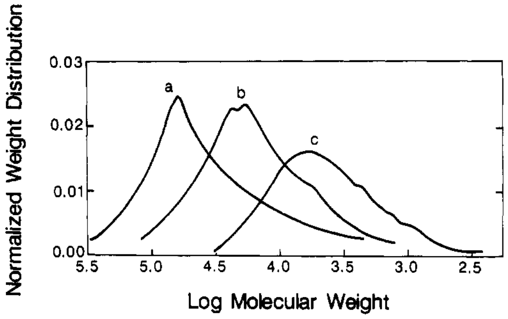


Figure 7. Change in molecular weight distribution of poly(1,4-phenylenediproprionic acid anhydride) (7) in chloroform as a function of time: (a) 0 h; (b) 24 h; (c) 72 h.

failed to form a linear chain.

Comparison. The weight-average molecular weight distribution of poly(sebacic anhydride) obtained from the three different methods of synthesis is shown in Figure 6. For this polymer, melt-polycondensation appeared to be superior. It is necessary to characterize the polymers immediately after synthesis. The polymer was unstable even in chloroform. Shown in Figure 7 is the change in molecular weight of the melt-polycondensed poly(1,4-phenylenedipropionic anhydride) (7 in Table I) in chloroform with time. The decay was even more rapid in tetrahydrofuran. In storage of the polymer powder in a closed vial, the M_n dropped from 7900 to 1300 in 4 weeks.

Discussion

When the three reaction schemes are compared, it is evident that melt-polycondensation produced the highest molecular weight. It should be considered the method of choice provided the monomers or polymers are thermally stable. However, each of the other two methods has its own merits.

Poly(terephthalic anhydride) (PTA) is an example showing the advantage of the Schotten–Baumann condensation. PTA has a T_g of 245 °C and a T_m of 372 °C.[14] Conducting the melt-polycondensation at such a high temperature often results in a charred product. The polymer can instead be prepared at room temperature by the solution or the interfacial methods.

The advantage of the dehydrative coupling reaction is its simplicity. Neither prepolymer formation nor acylation conversion is required. It is a single-step, one-pot synthesis in which a decarboxylic acid monomer can be directly converted into the polymer. It can be conducted at low temperatures to accommodate monomers that cannot withstand harsh reaction conditions. With the coupling reagents examined, however, the molecular weight observed was lower than that of the other two methods. Although similar dehydrative coupling reactions are highly efficient in peptide and ester synthesis,[26] the anhydride bond is not as stable as the amides or esters, and consequently the driving force for elimination of the water molecule or the acylated catalyst derivative is not as strong. For the organophosphorus reagents, steric hindrance may come into play when the polymer chain has grown to a certain length and may limit the molecular weight obtainable. A more powerful coupling agent is needed to take advantage of this direct approach to synthesizing polyanhydrides. The problem often encountered in separating the product from the catalyst derivatives must also be overcome, although this workup problem is not unique to the dehydrative coupling reaction. The facile depolymerization due to hydrolysis has to be contended with in handling polyanhydrides.

The finding in regard to ring formation agrees with Carothers and Hill's report, which shows that adipic acid is the shortest aliphatic dicarboxylic acid polymerizable by melt-polycondensation.[3] Although only mild reaction conditions were used in the dehydrative coupling study, cyclization could not be avoided. Apparently only chain lengths greater than six carbons are energetically stable enough to prevail over cyclic anhydride formation.

The fact that anhydride formation is not as favorable as amide or ester formation means that there is potentially an interference problem in the synthesis. Monomers with functional groups containing active hydrogens would obstruct anhydride formation. In theory functional groups such as amines, hydroxyls, and sulfhydryls can be blocked before polymerization.[26] However, should eventual removal of the blocking groups be desired, it would be difficult to do so without evoking polymer degradation.

Conclusion

The present study examined the existing methods and new approaches of synthesizing polyanhydrides. Although each of the three polymerization methods has its own merits, the dehydrochlorination and the catalyzed dehydrative coupling reactions produced only low molecular weights. For melt-polycondensation, higher molecular weights were obtained with a prolonged polymerization time of over 24 h. However, the temperature must be carefully monitored to avoid extensive decomposition. Cross-linking occurred for the PCPP–SA copolymers as a result of vacuum distillation at 175 °C for 4 days. The dehydrochlorination between an acyl chloride and a carboxylic acid, on the other hand, could be conducted in solution at low temperatures. Best results were obtained when the reaction was conducted in a nonaqueous interfacial system composed of hexane and dimethylformamide. An even milder polymerization is the direct coupling of the carboxyl groups via dehydrative agents. The organophosphorus compounds bis[2-oxo-3-oxazolidinyl]phosphinic chloride and phenyl *N*-phenylphosphoroamidochloridate were the most effective. However, even with mild reaction conditions, only cyclic oligomers were formed from monomers with a chain length of less than six carbons. The facile hydrolytic depolymerization is the major obstacle in the synthesis and isolation of hydrophilic polyanhydrides in this study. However, polyanhydrides with high hydrolytic resistance should be obtainable in high molecular weights.

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Registry No. 1 (homopolymer), 26776-29-4; 2 (homopolymer), 106680-95-9; 2 (SRU), 106681-05-4; 3 (homopolymer), 90409-77-1;

3 (SRU), 101017-51-0; **4** (homopolymer), 106680-96-0; **4** (SRU), 106681-06-5; **6** (copolymer), 31471-36-0; **7** (homopolymer), 106680-97-1; **7** (SRU), 106681-07-6; **8** (homopolymer), 106680-98-2; **8** (SRU), 106681-08-7; (AA)(TC) (copolymer), 31764-36-0; (AA)(TC) (SRU), 106681-01-0; (SA)(TC) (copolymer), 106680-89-1; (SA)(TC) (SRU), 32031-88-2; (DD)(TC) (copolymer), 106710-14-9; (DD)(TC) (SRU), 106681-02-1; (TA)(TC) (copolymer), 90456-92-1; (TA)(TC) (SRU), 26913-45-1; (SA)(PC) (copolymer), 106680-90-4; (SA)(PC) (SRU), 106681-03-2; (SA)(IC) (copolymer), 106680-91-5; (SA)(IC) (SRU), 106681-04-3; (SA)(FC) (copolymer), 106680-92-6; (SA)(FC) (SRU), 106710-15-0; (GA)(GC) (copolymer), 106680-93-7; (GA)(GC) (SRU), 26968-28-5; (SA)(SC) (copolymer), 106680-94-8; (SA)(SC) (SRU), 26913-47-3; (SA)(1,3,5-benzenetricarboxylic acid) (copolymer), 106680-99-3; $(H_3CCH_2)_3N$, 121-44-8; $(C_6H_5O)_2P(O)Cl$, 2524-64-3; $C_6H_5NHP(O)(Cl)OC_6H_5$, 51766-21-3; pyridine, 110-86-1; *N*,*N*-bis[2-oxo-3-oxazolidinyl]phosphinic chloride, 68641-49-6; 2,6-lutidine, 108-48-5.

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Synthesis and High Hole Mobility of Isotactic Poly(2-*N*-carbazolylethyl acrylate)

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ABSTRACT: Isotactic poly(2-*N*-carbazolylethyl acrylate) was synthesized by using ethylmagnesium chloride–benzalacetophenone as catalyst. The polymer showed crystallinity by X-ray diffraction. The temperature and electrical field dependence of hole drift mobility was measured by the time-of-flight method. The room-temperature mobility (1.7×10^{-5} cm^2/(V·s) at 2×10^5 V/cm) was considerably higher than that of both atactic polyacrylate and poly(*N*-vinylcarbazole) and is one of the highest mobility values reported for a photoconductive polymer. The origin of this result is discussed in a model for hopping transport between localized sites.

Introduction

Photoconductive polymers have been extensively studied since they are widely used in electrophotography and are potentially suitable for other electrodevices.[1-3] Most investigations have concentrated on a search for chromophores that are of high efficiency. Few studies have dealt with the effect of polymer structure.[4] There are two kinds of photoconductive polymers. One is a molecularly doped polymer, and the other is a polymer in which the chromophores are attached to the backbone through chemical bonds. In most cases, the former materials exhibit higher carrier mobilities than the latter type polymers.[5,6] One possible reason is that the molecular mobility of the chromophores is depressed due to the linkage between the chromophore and the polymer backbone. High carrier mobility can be expected for linkage-type polymers having higher chromophore contents than for molecularly doped polymers if several drawbacks could be excluded. In fact, poly(*N*-carbazolylpropylene oxide)[7] and poly(2-*N*-carbazolylethyl acrylate),[8] which have relatively low T_g's, exhibited high hole mobilities.

For hopping transport among a set of localized sites, the factors determining the drift mobility are the nature of the chromophore, the concentration, and the energy-state distribution.[9] The site energy distribution in completely disordered materials may be related to the "frozen-in disorder" which is introduced during the course of film formation. Thus, the site energy distribution may be narrower for polymers with lower T_g values, leading to higher drift mobility.

An alternative strategy to average the site energy distribution would be to introduce order by alignment of the chromophores. This can be achieved in stereoregular polymers which may be crystalline. In this investigation, we have succeeded in stereoregular polymerization of 2-*N*-carbazolylethyl acrylate by use of an anionic catalyst, producing the completely isotactic polyacrylate which has good film-forming properties. The hole-transport characteristics of the isotactic polyacrylate were compared with those of the corresponding atactic polymer. It is demonstrated for the first time that the highly controlled stereoregularity of a polymer backbone gives rise to pendant-type photoconductive polymers with high carrier mobility.

Experimental Section

Synthesis of Monomers. *N*-(2-Hydroxyethyl)carbazole (1). A solution of carbazole (10 g, 0.06 mol) in 100 mL of dry dimethylformamide (DMF) was vigorously stirred at 0 °C and treated with 4.32 g (0.072 mol) of sodium hydride oil dispersion

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