Carboxyl-Containing Polyesters and Polyurethanes from Dibenzyl L-Tartrate

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Synopsis

We have prepared polyesters from succinyl chloride, adipoyl chloride, and telephthaloyl chloride with dibenzyl L-tartrate, polyurethanes from hexamethylene diisocyanate, toluene 2,4-diisocyanate, and methylene-bis(4-phenyl isocyanate) with dibenzyl L-tartrate. The molecular weights of these polymers were generally low except for one of the polyurethanes. These polymers were reduced to give those having carboxyl side groups. Potency for inducing interferon was tested for one of the polymers. The result was not encouraging in showing low activity.

INTRODUCTION

Natural and synthetic polyanions often inhibit bacteria, fungi, viruses, and tumors, and this inhibition is of clinical importance and vital to our understanding of both normal and malignant growth.[1] These biologically active polyanions bind cells together in connective tissue and/or intracellular matrix.[2] The ability to induce interferon and the antiviral resistance of some polyanions, such as divinyl ether–maleic anhydride copolymer (pyran copolymer), poly(acrylic acid), poly(methacrylic acid), and oxyamylose have been reported.[3,4] Some polyanions such as pyran copolymer, poly(acrylic acid), poly(methacrylic acid), and poly(vinyl sulfate) are reported to be interferon-inducing, i.e., they promote the production of interferon by living organisms. Interferon is a potent growth inhibitor of virus, and its possibility as an effective anticancer drug is the subject of current enthusiasm.

The synthetic polyanions mentioned above are not biodegradable *in vivo*, and their long-term persistence in cells make them unsuitable interferon inducers for possible clinical use in man. Polyesters and polyurethanes, which are the subjects of this paper, have been used as biomedical materials with limited stability. They may undergo degradation after some time to be replaced by newly born tissues. Oligoesters and polyesters prepared from aliphatic compounds are known to undergo extensive hydrolytic cleavage *in vitro* under conditions of bacterial attack with otherwise mild conditions.[2,5] The desirable degradation of a polymer in the organism would proceed via hydrolysis and via resorption

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TABLE I
Reactions of Dibenzyl Tartrate with Dichlorides[a] and Diisocyanates[b]

Sample code	Dichloride or diisocyanate	Molar ratio to tartrate	Yield (%)	$[\eta]^c$ (dL/g)
SCL-B	succynyl chloride	1.11	85	0.06
ACL-B	adipoyl chloride	1.11	96	0.08
TCL-B	terephthaloyl chloride	1.11	64	0.05
HDI-B	hexamethylene diisocyanate	0.91	78	0.18
MDI-B	methylene bis(*p*-phenyl isocyanate)	0.91	98	0.08
TDI-B	toluene-2,4-diisocyanate	0.91	89	0.07

[a] Reaction conditions: at 50–80°C for 3 h and at 160°C for 8 h.
[b] Reaction conditions: at 160°C for 3 h.
[c] Measured in DMF at 30°C.

by phagocytory cells. After polyesters and polyurethanes have been implanted in the living organism, intensive hydrolytic cleavage sets in after a few weeks.

EXPERIMENTAL

Acid Chlorides. Commercially available succinyl chloride and adipoyl chloride were purified by distillation. Telephthaloyl chloride was recrystallized from *n*-hexane.

Isocyanates. Methylene bis(4-phenyl isocyanate), hexamethylene diisocyanate, and toluene-2,4-diisocyanate available commercially were purified by distillation.

Dibenzyl L-Tartrate. Dibenzyl L-tartrate was obtained by the reaction of L-tartaric acid according to the literature.[6] Dibenzyl L-tartrate was precipitated with petroleum ether, and was purified by repeated recrystallization by ethyl ether–petroleum ether. (mp 50–51°C/lit. 50°C) [C, 65.28%; H, 5.46%, (calcd: C, 65.45%; H, 5.45% for $C_{18}H_{18}O_6$].

Polycondensation. An example of preparation of polyesters is as follows.

TABLE II
Elemental Analysis of Polymers

Sample code	Elemental analysis (calcd) C %	H %	N %
SCL-B	63.57	4.69	—
	(64.07)	(4.85)	(—; $C_{22}H_{20}O_8$)
ACL-B	65.06	5.43	—
	(65.45)	(5.45)	(—; $C_{24}H_{24}O_8$)
TCL-B	66.52	4.33	—
	(67.82)	(4.35)	(—; $C_{26}H_{20}O_8$)
HDI-B	66.44	5.68	5.09
	(68.27)	(4.86)	(4.82; $C_{26}H_{30}N_2O_8$)
MDI-B	62.19	6.27	5.73
	(62.64)	(6.07)	(5.62; $C_{33}H_{28}N_2O_8$)
TDI-B	62.24	5.11	5.23
	(64.28)	(4.79)	(5.55; $C_{27}H_{24}N_2O_8$)

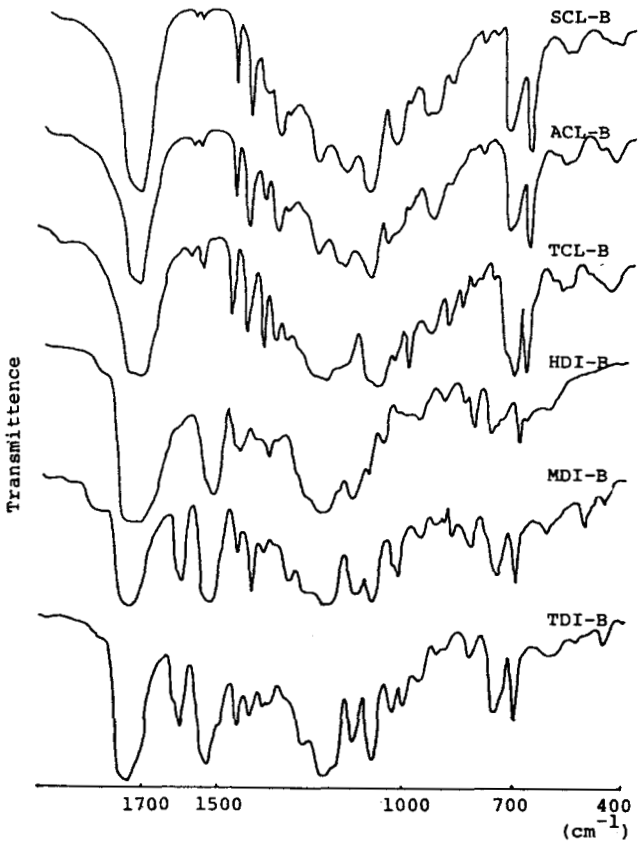


Fig. 1. IR spectra of polymers.

A mixture of dibenzyl L-tartrate (16.7 g, 5 mmol) and succinyl chloride (7.1 g, 4 mmol) was allowed to react at 50°C for 3 h and then at 160°C for 8 h. Nitrogen was introduced continuously into the mixture to release hydrogen chloride. From the reaction mixture dissolved in ethyl acetate, the polyester (SCL-B) was precipitated by the addition of *n*-propanol. Polycondensations of dibenzyl L-tartrate with adipoyl chloride (ACL-B) and telephthaloyl chloride (TCL-B) were carried out in a similar way.

Polyaddition. An example of the polyaddition is as follows. A mixture of dibenzyl L-tartrate (15.2 g, 0.46 mmol) and methylene-bis(4-phenyl isocyanate (21.7 g, 0.50 mmol) was allowed to react at 160°C for 3 h. The reaction mixture was dissolved in dioxane and polyurethane (MDI-B) was precipitated by adding *n*-propanol. Polyaddition reactions of dibenzyl L-tartrate with hexamethylene diisocyanate (HDI-B) and toluene 2,4-diisocyanate (TDI-B) were carried out in a similar way.

Reduction of the Polymer. The polymers with dibenzyl protecting group were reduced to polymers having carboxyl groups by catalytic hydrogenation on Palladium Carbon. An example of the reduction was as follows: SCL-B (1 g), dissolved in ethyl acetate (40 mL), was reduced by hydrogen with Palladium Carbon (100 mg) for 6 h at room temperature and under atmospheric pressure. Polymers having carboxyl groups (SCL-C) were isolated from the filtered solution

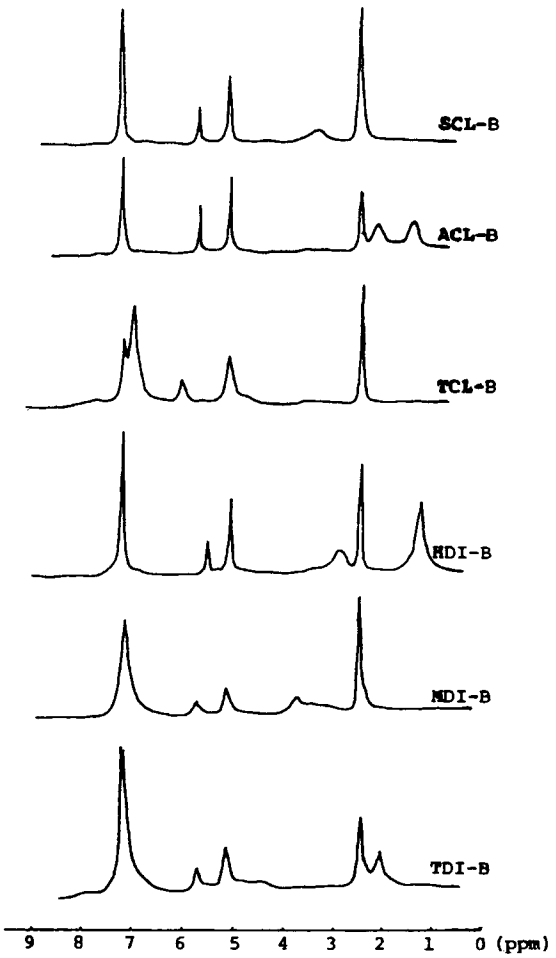


Fig. 2. NMR spectra of polymers.

by adding *n*-hexane. Other polymers (ACL-C, TCL-C, MDI-C, TDI-C, and HDI-C) containing carboxyl groups were obtained in a similar way.

ANALYTICAL METHODS

^{1}H NMR. ^{1}H NMR spectra were taken for the 10 wt % solutions of the polymers in DMSO-d_6 on a 60 MHz with a JNM-C 60 HL Spectrometer at room temperature. TMS was used as a standard.

Infrared Spectra. Infrared spectra were obtained by KBr disk method on a Hitachi Infrared Spectrometer, Model EPI-G_3.

GPC Measurements. The gel permeation chromatography was carried out on a Toyo Soda Model HLC-802UR liquid chromatograph with columns [pre-column–TSK gel GMSP + GMH6 ($\frac{3}{8}$ in., 2 ft) × 2]. Solvent concentration was 1 vol %, and the sample injected was 100 μL.

Interferon Assay.[7,8] Interferon assay, which was performed by the courtesy of Dr. H. Saito of Sagamihara National Hospital, was carried out by a plaque

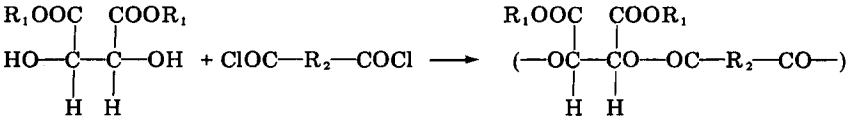
TABLE III
Solubilities of Polymers[a]

Sample code	Dimethyl sulfoxide	Tetra hydrofuran	Acetic acid	1*N* NaOH	Water
SCL-B	++	++	+	−	−
SCL-C	++	++	+	++	+
ACL-B	++	++	+	−	−
ACL-C	++	++	+	++	+
TCL-B	++	++	+	−	−
TCL-C	++	++	+	+	−
HDI-B	++	++	++	−	−
HDI-C	++	++	++	+	−
MDI-B	++	+	−	−	−
MDI-C	++	+	−	+	−
TDI-B	++	+	+	−	−
TDI-C	++	+	+	+	−

[a] ++ = soluble; + = slightly soluble; − = insoluble.

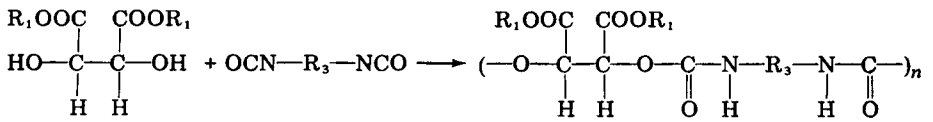
reduction method on mouse-L-cell monolayers employing vesicular stomatitis virus (VSV) as the challenge virus. The titer of antiviral activity was expressed as reduced by 50% of the number of virus plaques which developed on control plates (PRD_{50}).

RESULTS AND DISCUSSION



$R_1 = CH_2(C_6H_5)$, $R_2 = (CH_2)_2$ for SCL-B $(CH_2)_4$ for ACL-B
C_6H_4 for TCL-B

All the products were soluble in ethyl acetate and could be purified by reprecipitation with *n*-propanol. The obtained polymers were white solid materials. The hydrogen chloride formed was removed by continuous introduction of nitrogen into the mixture. The molar ratio of dibenzyl L-tartrate and the chloride was kept at 0.9:1.0. Polyaddition of dibenzyl L-tartrate and various diisocyanates were carried out in a similar way to the literature[9] (see Table I).



$R_1 = CH_2(C_6H_5)$, $R_3 = (CH_2)_6$ for HDI-B, $CH_2(C_6H_4NCO)_2$
for MDI-B $(CH_3)C_6H_3(NCO)_2$ for TDI-B

All the reaction products were soluble in dioxane, and the polyurethanes were precipitated from the dioxane solutions with *n*-propanol. The obtained polyurethanes were white or slightly yellowish solid materials. Elemental analyses of all the polyesters and polyurethanes shown in Table II agree with the theo-

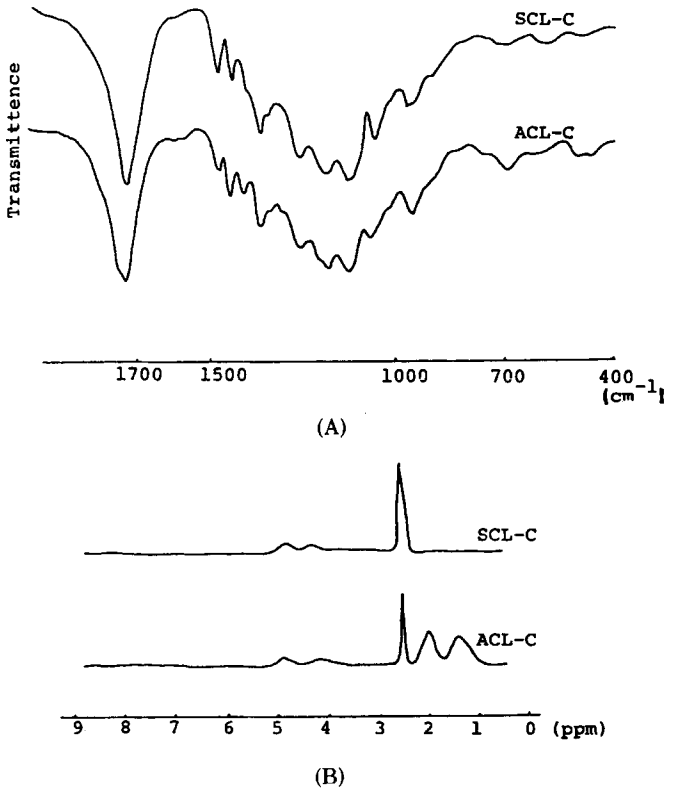


Fig. 3. IR (A) and NMR (B) spectra of reduced polymers.

retical values. Infrared spectra of the polymers are shown in Figure 1. Both polyesters and polyurethanes exhibit absorption bands at 1720–1700 cm^{-1} characteristic of carbonyl (ester) stretching and absorption at 690 cm^{-1} characteristic of 1-substituted aromatic groups. Polyurethanes show N–H stretching at 3500 cm^{-1} and amide II band at 1650 cm^{-1}.

NMR spectra of the polymers are shown in Figure 2. All the spectra show signals at 7.20 ppm due to the aromatic protons of the benzyl group. Other signals are assigned to hydrogen atoms on main chain carbons. The degrees of polymerization were estimated from the viscosities in dimethyl formamide at 30°C. A polymer having an intrinsic viscosity of 0.18 was obtained by polyaddition of hexamethylene diisocyanate (HDI-B). The viscosities of other polymers were generally low. The gel permeation chromatograms of the polymerization products were measured. The molecular weight 1.02×10^4 of standard polystyrene samples eluted at 80 counts. These polymers eluted at 80–100 counts. These results show the molecular weight of these polymers are generally low. All the polymers containing benzyl ester groups were reduced by hydrogenation of palladium carbon to polymers with carboxyl groups. The molecular weight of these polymers might be slightly reduced by the hydrogenation treatment. Table III shows the results of solubility test before and after the reduction. All the polymers after the reduction were soluble in 1*N* NaOH, and two of them were soluble in water. Complete reduction was confirmed by the

infrared spectra by the disappearance of 690 cm^{-1} peak due to the 1-substituted aromatic residues (see Fig. 3). Merigan et al. have reported the antiviral activity shown by the serum from the mouse injected with polyanions including poly(acrylic acid) was due to interferon induced by polyanions.[10] In this work, the activity of interferon induction by SCL-C (one of water-soluble hydrogenated polymers) as well as those of atactic poly(acrylic acid) and isotactic poly(acrylic acid) were studied. SCL-C failed to induce detectable levels of circulating interferon in STD-ddy mice assayed at 2,4 or 24 h after administration. This result might be due to the mouse strain used or the lower molecular weight of polymer.

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