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Synthesis of Novel Biodegradable Poly(amide-Ester)s from Penicillin

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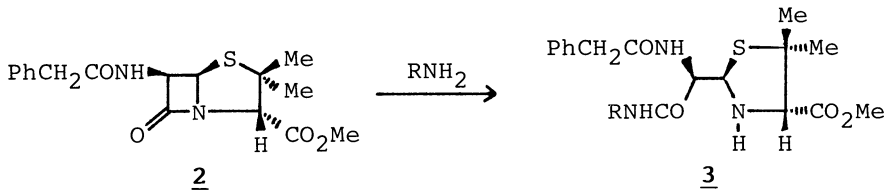
Novel biodegradable poly(amide-ester)s were successfully synthesized from antibiotic penicillin, utilizing a nucleophilic addition of primary amines to the β-lactam ring of penicillin.

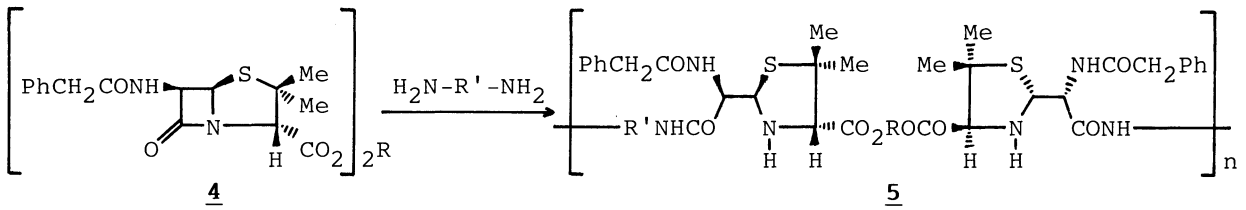
Increasing public concern about the treatment of waste materials has stimulated the study of the biodegradation of synthetic polymers.[1] Poly(vinyl alcohol),[2] poly(ether)s,[3,4] poly(amide)s,[5-7] poly(ester)s,[8-11] and poly(urethane)s,[12] are known to be susceptible to biological degradation. Among them, poly(ester)s are the most biodegradable polymers, by both micro organisms[8,9] and enzymes.[10,11] The degradability of poly(ester)s depends mainly on their chemical structure: only aliphatic poly(ester)s are known to be attacked by hydrolytic enzymes of some micro organisms.[10,11] Unfortunately, however, the softening points of aliphatic poly(ester)s are too low to permit their use as a material in various fields. Several recent efforts have accordingly been focused on the preparation of poly(ester)s with higher melting points, which randomly contain, for example, an amide[12] or an aromatic group[13] in the main chain in addition to the aliphatic ester residue as a biodegradable repeating unit. Here we report the synthesis of new polymers whose main chain alternately contains ester and amide residues of α-amino acids, using a readily available dipeptidyl antibiotic agent, penicillin G (**1**),[14] as one of starting materials.

It has been well-known that penicillin is ready to an addition of strong nucleophiles to its β-lactam ring.[15] For example, a methyl ester of **1** (**2**) and equimolar aliphatic primary amines in dichloromethane give addition products (**3**) of asymmetry retention in moderate yields although it takes a long reaction time (several days):[16]



2 **3**

If this addition reaction proceeded more efficiently, one could utilize it to an addition polymerization by using a pair of bifunctional comonomers, **4** and diamine:



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We therefore undertook the addition reaction of **2** with butyl- or benzylamine in various solvents as a model reaction for polymer synthesis, and it was found that the reaction proceeded the most smoothly in N,N-dimethylformamide (DMF) without any side reaction products (Table 1), which consequently shows that the ring-opening addition can be applied for polymer synthesis. Next, three monomers (**4**) were synthesized from a potassium salt of **1** and α,ω-dibromides by the direct esterification in DMF[17] (Table 2).

Table 1. Reaction of **2** with RNH_2 in DMF[18]

R	Product	Time/h	Yield/%
Butyl	**3a**	3	98.3
Benzyl	**3b**	7	96.5

Table 2. Synthesis of monomers from potassium salt of **1** and Br-R-Br[a]

R	Monomer	Yield/%	$[\alpha]_D$[b]/°
$(CH_2)_4$	**4a**	96.7	+228
$(CH_2)_6$	**4b**	93.7	+226
CH_2-p-C_6H_4-CH_2	**4c**	90.2	+237

a) For reaction and workup procedures, see Ref. 19; for spectral data, Ref. 20. b) Measured in chloroform (c 1).

The polyaddition was then carried out employing the obtained monomers (1.00 mmol) and 1,6-diaminohexane or 1,4-bis(aminomethyl)benzene (1.00 mmol) in DMF at room temperature for 24 h, to afford an almost quantitative amount of the polymers as colorless solids insoluble in 2-propanol (Table 3).

Table 3. Polymerization of **4** and H_2N-R'-NH_2[a]

Monomer	DMF/mL	R'	Polymer	Yield/%	$\overline{Mn}$	Tg/°C	Td/°C	$[\alpha]_D$[b]/°
4a	2	$(CH_2)_6$	**5a**	98.1	3440	103	210	+66.7
4a	4	CH_2-p-C_6H_4-CH_2	**5b**	82.5	2980	112	217	+89.7
4b	2	$(CH_2)_6$	**5c**	94.8	2880	96	204	+62.1
4b	4	CH_2-p-C_6H_4-CH_2	**5d**	77.0	2980	104	218	+85.8
4c	4	$(CH_2)_6$	**5e**	93.2	3190	111	194	+71.4
4c	4	CH_2-p-C_6H_4-CH_2	**5f**	87.7	4060	120	215	+89.7

a) See text. b) Measured in DMF (c 1).

Number average molecular weights ($\overline{Mn}$'s) of the obtained polymers were measured by vapor pressure osmometry in N,N-dimethylacetamide (DMAc); glass transition temperatures (Tg's) and decomposition onset temperatures (Td's) were estimated with a differential scanning calorimeter at a scan rate of 5 K/min under nitrogen. Tg's and Td's are sufficiently high as expected, and further, the polymers will be du-

rable to various processing since the difference between these two temperatures are about 100 K. Moreover, we found that the polymers possess good film-forming properties (e.g., they can be cast from their DMAc solutions) in spite of their rather low molecular weights. In addition to these satisfactory characteristics, it was expectantly found that the polymers undergo biodegradation by soil bacteria: three strains of Pseudomonas putida were isolated from six independent Japanese soil by using a mineral-agar plate overlayered by one of the obtained polymers (**5a**) as a sole carbon source. Isolation and characterization of soil bacteria, and biodegradability evaluation using these polymers will be published elsewhere.[21]

In conclusion, processable and biodegradable poly(amide-ester)s, whose diamine and diol units could be replaced to meet physical requirements, were successfully synthesized from penicillin G (**1**), utilizing the quantitative addition reaction of primary amines to the β-lactam ring.

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14) According to the I.U.P.A.C. nomenclature, **1** is named [2S,5R,6R]-6-phenylacetylamino-1-aza-3,3-dimethyl-7-oxo-4-thiabicyclo[3.2.0]heptane-2-carboxylic acid.
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18) Reaction procedure. To a solution of **2** (0.500 mmol) in DMF (1 mL) was added 0.500 mmol of an amine at room temperature. The reaction progress was monitored by t.l.c. To the solution was added ethyl acetate (30 mL), followed by washing with water (3 x 30 mL) and drying over magnesium sulfate. Column chromatography over silica gel eluting with chloroform - ethyl acetate (2:1) afforded **3a** or **3b** whose spectral data agreed with those of the authentic ones in Ref. 16. In addition, since the products are amino-esters and hence there is the possibility of self-decomposition, the reaction period was extended up to a week to examine the stability of the products; it was found that they were sufficiently stable by t.l.c. We therefore assume that no decomposition occurred during polymerization for 24 h.

19) To a stirring suspension of Penicillin G potassium salt (25.0 mmol) in DMF (50 mL) was added an α,ω-dibromide (10.0 mmol), and stirring was continued for 24 h. After adding water (70 mL), the reaction mixture was extracted with ethyl acetate (3 x 100 mL), washed with water (4 x 100 mL), brine (100 mL), dried over magnesium sulfate, and evaporated to dryness under vacuum below 30°C. The oily residue was subjected to silica gel column chromatography (chloroform - ethyl acetate, 4:1), and the monomer (**4a**, **4b**, or **4c**) was obtained as a colorless crystal.

20) **4a**: mp 38°C; ^{1}H NMR ($CDCl_3$) δ 7.39-7.28(m, 10H), 6.08(d, J=9 Hz, 2H), 5.65(dd, J=9, 4 Hz, 2H), 5.50(d, J=4 Hz, 2H), 4.36(s, 2H), 4.23-4.11(m, 4H), 3.64(s, 4H), 1.75-1.73(m, 4H), 1.43(s, 6H), 1.42(s, 6H); IR (KBr) 1785, 1745, 1665 cm^{-1}; MS, m/e 723 [M^++1].
4b: mp >30°C; ^{1}H NMR ($CDCl_3$) δ 7.39-7.28(m, 10H), 6.11(d, J=9 Hz, 2H), 5.65(dd, J=9, 4 Hz, 2H), 5.50(d, J=4Hz, 2H), 4.36(s, 2H), 4.20-4.07(m, 4H), 3.64(s, 4H), 1.66-1.60(m, 4H), 1.44(s, 6H), 1.43(s, 6H), 1.40-1.38(m, 4H); IR (KBr) 1780, 1740, 1665 cm^{-1}; MS, m/e 751 [M^++1].
4c: mp 49°C (Tg); ^{1}H NMR ($CDCl_3$) δ 7.38-7.25(m, 14H), 6.05(d, J=9 Hz, 2H), 5.63(dd, J=9, 4 Hz, 2H), 5.48(d, J=4Hz, 2H), 5.16(AB, 4H), 4.39(s, 2H), 3.63(s, 4H), 1.40(s, 6H), 1.35(s, 6H); IR (KBr) 1780, 1740, 1665 cm^{-1}; MS, m/e 771 [M^++1]. All the monomers gave satisfactory elemental analyses.

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