Chemoselective Dehydration Polycondensations of Dicarboxylic Acids and Diols Having Pendant Hydroxyl Groups Using the Room Temperature Polycondensation Technique

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Introduction. The impetus for research in the area of aliphatic polyesters over the past 20 years has centered on the need for efficient synthesis of functional polyesters because they are of interest to polymer science and biomedical fields. Aliphatic polyester is known as the most promising category of biodegradable polymers and environmentally benign materials. However, most aliphatic polyesters are hydrophobic and are therefore not applied to biomedical applications because of the lack of desirable hydrophilicity and reactive pendent functionalities.

Introduction of a polar functional group into polyester enabled the application of these materials to construction of novel controlled drug delivery systems and functional vectors as well as related biomedical applications.[1] Generally, chemical synthesis of linear polyesters having pendent hydroxyl groups is difficult because it requires a multistep reaction pathway including tedious protection and deprotection of the functional groups of the monomer units, which often engender degradation of the polymer backbone. For example, Cao et al.[2,3] reported a simple protection and deprotection strategy to prepare aliphatic polyesters having pendent reactive hydroxyl groups, i.e., poly(butylene succinate-*co*-butylene malate)[2] and poly(butylene tartrate).[3] During deprotection, undesirable degradation and gelation occurred.[3] The necessity for protection of functional groups during the reaction lies in the nonspecific nature of chemical synthesis. Russell et al.[4] reported a one-step synthesis to prepare polyesters having pendent hydroxyl groups via enzyme-catalyzed polycondensation of various triols and divinyl adipate. Recently, Gross et al.[5] also prepared poly(sorbityl adipate) via a biocatalyzed regioselective polycondensation of sorbitol and adipic acid. However, because these approaches are actually based on high selectivity between the monomer substrates and enzyme catalysts, the number and species of usable monomers were limited. Although another simple way to address regioselectivity in polycondensation is kinetic control of primary alcohol and secondary alcohol, polycondensation of diols and dicarboxylic acid has been generally performed at >250 °C.[6]

Recently, we reported room temperature direct polycondensation of dicarboxylic acids with diols that had been catalyzed using rare-earth trifluoromethanesulfonate[7] to afford aliphatic polyesters with M_n of $>1.0 \times 10^4$. This polycondensation system under mild conditions made it possible to use thermally unstable monomers containing a carbon−carbon double bond and bromo functionality.[8] These findings prompted us to explore a new one-step strategy to synthesize polyester containing reactive hydroxyl groups by polycondensation of diols and dicarboxylic acids having secondary hydroxyl groups under kinetic control.

In this presentation, we describe the one-step synthesis of polyesters having pendent hydroxyl groups by chemoselective polycondensation of several diols and dicarboxylic acids having pendent hydroxyl groups including tartaric acid (TA)[9] and malic acid (MA) under mild conditions, using rare-earth trifluoromethanesulfonates including scandium [$Sc(OTf)_3$], yttrium [$Y(OTf)_3$], samarium [$Sm(OTf)_3$] ytterbium trifluoromethanesulfonates [$Yb(OTf)_3$], and scandium trifluoromethanesulfonimide [$Sc(NTf_2)_3$].[10]

Results and Discussion. As a model reaction of regioselective esterification, direct esterification of carboxylic acid containing a pendent secondary hydroxyl group, 3-hydroxybutyric acid, and equimolar ethanol was carried out at 40 °C for 10 h in the presence of 0.5 mol % of $Sc(OTf)_3$ (Supporting Information). Expectedly, esterification of the primary alcohol proceeded chemoselectively (conversion: 60%; chemoselectivity: >99%).

Results of the reaction of diols and dicarboxylic acids are shown in Table 1; they agree with the formation of polymer according to the mechanism of step polymerization. First, we performed bulk polycondensations of dicarboxylic acid having one hydroxyl group per monomer unit, MA and diols. The number-average molecular weights (M_ns) were estimated using size exclusion chromatography (SEC) with $CHCl_3$ as the eluent (polystyrene standards). The polycondensations with 1,9-nonanediol (1,9-ND) were carried out under reduced pressure (0.3−3 mmHg) using $Sc(OTf)_3$. At 80 °C, the one-step direct polycondensation proceeded to afford linear poly(nonamethylene DL-malate) with $M_n = 13.1 \times 10^3$ for 7 h in the presence of 0.5 mol % catalyst (99% yield, run 1 in Table 1). From the ^{1}H and ^{13}C NMR spectra, the presence of both hydroxyl and carboxylic end groups was confirmed. As another example to illustrate the mildness of the polycondensation, we present polycondensation using dicarboxylic acid having two hydroxyl groups per monomer unit, L-TA. Polycondensations with 1,9-ND and 1,7-heptanediol were carried out at 60 °C using 0.5 mol % of $Sc(OTf)_3$ to give polyester with $M_n = 8.3 \times 10^3$ and 7.3×10^3 (81 and 85% yield after reprecipitation, runs 3 and 4). Fortunately, peaks ascribed to reaction of secondary hydroxyl groups were observed in neither ^{1}H nor ^{13}C NMR spectra (Supporting Information); i.e., the lower temperature direct polyesterification of dicarboxylic acids containing hydroxyl groups with diols enabled one-step synthesis of polyester having hydroxyl functionality in excellent yields. In optical rotation measurements of poly(nonamethylene L-tartrate) in $CHCl_3$, the molecular rotation $[\phi]^{20}_D$ was 20.7, which agrees with that of L-TA, $[\phi]^{20}_D = 22.7$. The result indicated that racemization hardly occurred during polycondensation. In addition, DSC measurement indicated that the respective glass transition temperature (T_g) and melting temperature (T_m) of poly(nonamethylene L-tartrate) were −11 and 59 °C.

To optimize experimental conditions, we surveyed the Lewis acids including $Y(OTf)_3$, $Sm(OTf)_3$, and $Yb(OTf)_3$ in the polycondensation of L-TA and 1,9-ND [run 5; $Yb(OTf)_3$]. However, the M_ns (2.3×10^3−4.4×10^3) were lower than that of the polyester synthesized with $Sc(OTf)_3$ as the catalyst. On the other hand, higher temperature (at 80 °C) and higher Lewis acidity of $Sc(NTf_2)_3$ (run 2) induced gelation because of nonspecificity of the primary and secondary alcohols. Ternary

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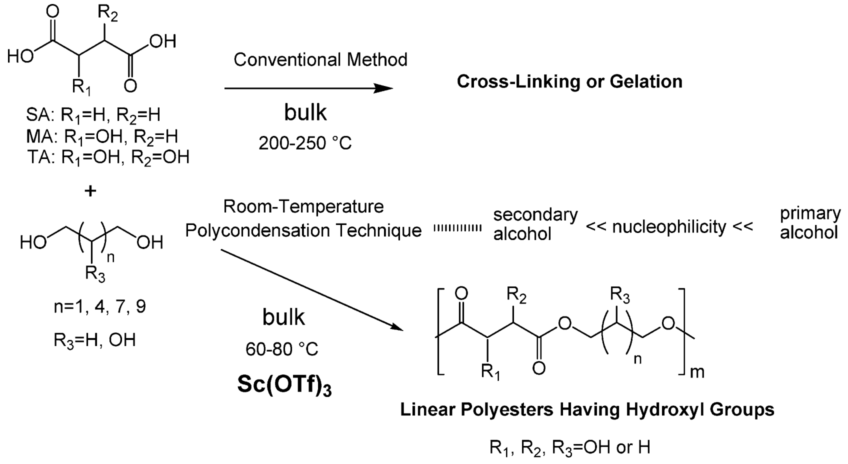
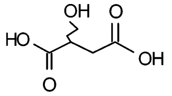
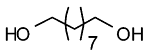
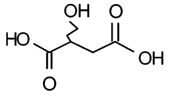
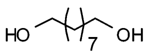
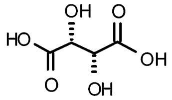
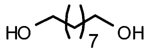
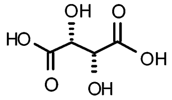
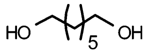
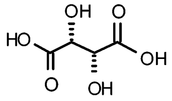
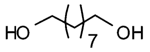
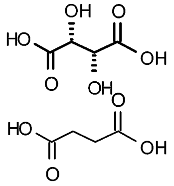
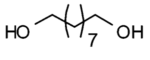
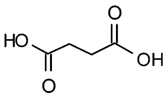
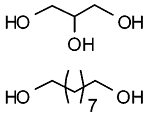
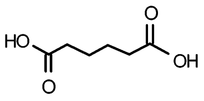
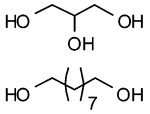
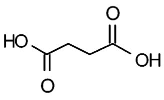
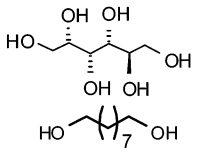
Scheme 1. Chemoselective Dehydration Polycondensations of Dicarboxylic Acids and Diols Having Pendent Hydroxyl Group



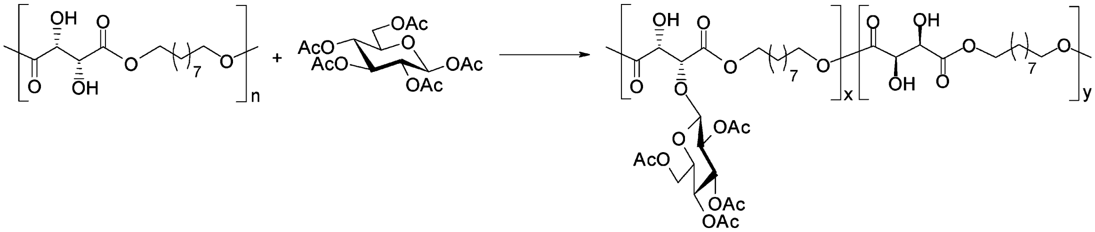
polycondensation of L-TA and SA with 1,9-ND was also performed to control the hydroxyl content. The polycondensation

Table 1. Lower Temperature Direct Polycondensations of Dicarboxylic Acids and Diols Having Pendent Hydroxyl Groups[a]

run	dicarboxylic acid	diol	catalyst	temp. °C	time h	yield %	M_n[b] x 10^{-3}	M_w/M_n[b]
1			$Sc(OTf)_3$	80	7	> 99[c]	13.1	2.22
2			$Sc(NTf_2)_3$	60	7	gelation	—	—
3			$Sc(OTf)_3$	60	12	> 99[c] (81[d])	8.3	1.68
4			$Sc(OTf)_3$	60	30	> 99[c] (85[e])	7.3	3.19
5			$Yb(OTf)_3$	60	125	84[d]	4.4	2.22
6[f]			$Sc(OTf)_3$	60	20	> 99[c]	13.0	1.77
7[g]			$Sc(OTf)_3$	60	10	> 99[c]	18.6	2.38
8[g]			$Sc(OTf)_3$	60	10	> 99[c]	26.2	4.24
9[g]			$Sc(OTf)_3$	60	20	99[c]	10.0	2.18

[a] All runs are performed by bulk polycondensation ($[catalyst]_0$ = 0.5 mol %) under reduced pressure (0.3−3.0 mmHg). [b] Determined by SEC measurement in $CHCl_3$ (except for run 4) and in DMF (run 4) relative to poly(styrene)s. [c] Without reprecipitation. [d] After reprecipitation using $CHCl_3$ and Et_2O. [e] After reprecipitation using acetone and Et_2O. [f] $[L\text{-TA}]_0/[SA]_0 = 1/9$. [g] $[Glycerol]_0/[1,9\text{-ND}]_0 = [D\text{-sorbitol}]/[1,9\text{-ND}]_0 = 1/4$.

Scheme 2. Glycosidation of Pendent Hydroxyl Groups in Linear Polyester



proceeded smoothly at 60 °C to give poly(nonamethylene tartrate-*co*-nonamethylene succinate) with M_n of 1.3×10^4 ($M_w/M_n = 1.77$) in a good yield (67%). The observed ratio from the ^{1}H NMR was identical to the targeted ratio ($[SA]_0/[\text{L-TA}]_0 = 9/1$). Ternary polycondensation of diols containing secondary hydroxyl groups including glycerol and sorbitol with dicarboxylic acids (runs 7−9) also proceed successfully to afford the corresponding polyesters ($M_n = 1.0 \times 10^4 - 2.6 \times 10^4$).

The next question to be examined is that of how chemical modification of the hydroxyl group is possible. Glycosidation of the pendent hydroxyl groups was carried out (Scheme 2 and Supporting Information). According to our previous procedures,[11] glycosidation of the hydroxyl group was performed in dichloromethane at 27 °C using glucose pentaacetate as the glycosyl donor and BF_3/Et_2O as the catalyst. The glycosidation proceeded smoothly to afford a sugar-containing polyester (50% glycosidation) in a good yield (80%).

Finally, cultivations of *Escherichia coli* (*E. coli*) as a model organism were carried out in the presence of $Sc(OTf)_3$, aimed for investigation of the toxicity. The cultivation curves (37 °C for 5 h) did not change in the range 0.1−1.0 g/L $Sc(OTf)_3$ concentration compared with that in the absence of the catalyst (Supporting Information). The results indicate lower toxicity of the catalyst toward organisms.

In this paper, we described direct polycondensations of dicarboxylic acids and diols having pendent hydroxyl groups catalyzed by $Sc(OTf)_3$ to afford a polyester having hydroxyl functionality ($M_n > 1.0 \times 10^4$) using a one-step procedure. The development of this polycondensation system is extremely effective not only for advanced material design using functional monomers but also for effective utilization of biomass resources.

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Supporting Information Available: NMR spectra and SEC charts of poly(nonamethylene L-tartrate) and poly(nonamethylene DL-malate) before and after glycosidation. This material is available free of charge via the Internet at http://pubs.acs.org.

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