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K. B. Wagener[a]; J. G. Linert[b]; J. E. O'gara[a]
[a] Department of Chemistry and Center for Macromolecular Science and Engineering, University of Florida, Gainesville, Florida [b] 3M Company, St. Paul, Minnesota

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LOW-TEMPERATURE POLYESTERIFICATION OF 3-HYDROXY-2-PHENYLPROPIONIC ACID

K. B. WAGENER,* J. G. LINERT,† and J. E. O'GARA

Department of Chemistry and Center for Macromolecular Science and Engineering
University of Florida
Gainesville, Florida 32611-2046

ABSTRACT

The synthesis of poly(3-hydroxy-2-phenylpropionic acid), prepared from tropic acid and 1,3-dialkylcarbodiimide (cyclohexyl or isopropyl) with *p*-toluenesulfonic acid (PTSA) and/or dimethylaminopyridine (DMAP) as catalysts, has been investigated. Molecular weight and yield have been found to vary inversely with temperature and solvent polarity. Dialkylcarbodiimide activation of the carboxylic acid is enhanced when PTSA and DMAP are used in equal concentrations. Highest molecular weights and yields were achieved at −20°C with 50% (mol% of monomer) DMAP and PTSA in a cyclohexane/THF solvent system.

INTRODUCTION

Polyester synthesis via direct condensation has traditionally found limited application because the high temperatures required to obtain high conversions often lead to side reactions which prevent high molecular weights from being obtained [1]. As monomers become more chemically demanding in design and stability, a need to prepare polyesters under mild reaction conditions has developed. At present, several low-temperature polyesterification systems are available [2–4]. Two particularly effective protocols have been developed by Moore and Stupp [3] and by Belcheva and coworkers [4]. They employ 1,3-dialkylcarbodiimides as activating

†Present address: 3M Company, St. Paul, Minnesota 55144-1000.

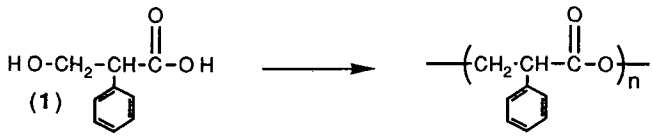

FIG. 1. Low temperature polycondensation of tropic acid.

agents when catalyzed by *p*-toluenesulfonic acid (PTSA), pyridine, dimethylaminopyridine (DMAP), or combinations thereof. These synthetic methodologies have already found application in the polymerization of chemically sensitive, optically active hydroxy acids [5, 6].

As part of our program to develop polystyrene telechelomers possessing hydroxy acid termini suitable for polyester condensation [7], we have undertaken an investigation of the low temperature (−20 to 40°C) polymerization of 3-hydroxy-2-phenylpropionic acid (**1**), tropic acid (Fig. 1).

The present results extend low-temperature polyesterification to polystyrene-type monomers. More particularly, the procedure provides an alternative condensation method for hydroxy-acid-terminated polystyrene telechelomers which are susceptible to decomposition using traditional high-temperature techniques [7]. As in previous reports, the low-temperature polymerization of tropic acid centers on carboxylic activation using 1,3-dicyclohexylcarbodiimide (DCC) or 1,3-diisopropylcarbodiimide (DiPC). Figure 2 describes the mechanism of action for DCC or its analog, DiPC [3, 4, 8].

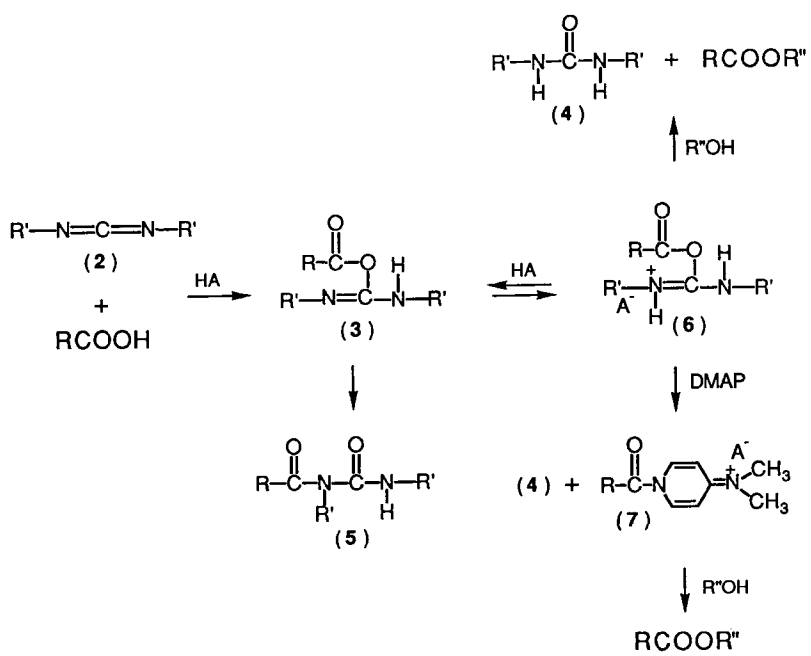

FIG. 2. Mechanism of ester formation using dialkylcarbodiimide activation with acid and nucleophilic base catalysts.

The carbodiimide (2) activates the carboxylic acid by forming an *O*-acylurea (3) which more easily combines with an alcohol to form an ester bond and a urea (4). However, the *O*-acylurea (3) may rearrange to a relatively inactive *N*-acylurea (5) which terminates the chain end and limits the formation of high molecular weight polymer. The protic acid catalyst, PTSA, is thought to hinder *N*-acylurea formation by protonating the *O*-acylurea [9]. One of the tautomeric forms of the protonated *O*-acylurea (6) places a positive charge on the imine nitrogen; the consequent decrease in nucleophilicity of the nitrogen can be expected to hinder the rearrangement to *N*-acylurea.

Pyridine or DMAP is thought to lower *N*-acylurea formation by reacting with the *O*-acylurea before rearrangement occurs to form an acylpyridinium cation (7), which can combine with an alcohol to form an ester linkage and regenerate pyridine or DMAP [3, 10]. Finally, we assume that as documented previously [3, 10], the carbodiimide reacts more rapidly with the acid as opposed to the alcohol, thereby avoiding any significant chain termination via alcohol coupling.

EXPERIMENTAL

General and Materials

^{1}H-NMR 200 MHz and ^{13}C-NMR 50 MHz spectra were recorded on a Varian XL-Series NMR Superconducting Spectrometer system. All NMR spectra were recorded in $CDCl_3$ with 1% v/v TMS as an internal reference. Resonances are reported in δ units downfield from TMS at 0.00 ppm. Polymer molecular weights were measured directly by using a ratio of the decoupled ^{13}C-NMR spectrum's integration assigned to the methylene carbon adjacent to the polymer's hydroxyl functionality on the end group (64.4 ppm, T_1 = 0.487 second) vs the integration of the aromatic carbon resonances between 130 and 127 ppm (T_1 = 0.212 second). The T_1 measurements were determined using the inversion recovery method [11]. The quantitative measurements used a 7-second delay between pulses and gated decoupling. Comparison of integrations completed using 7 and 10 seconds delays resulted in less than a 1% difference in the calculated molecular weight.

IR spectra were recorded on a Perkin-Elmer model 1600 FTIR spectrometer. Elemental analyses were performed by Atlantic Microlab, Norcross, Georgia. Size exclusion chromatography (SEC) data were recorded using a Waters Associates Liquid Chromatograph equipped with an RI detector. Listed molecular weight measurements of the products were determined vs polystyrene standards using THF as eluent. The resolution, produced by a coupled pair of columns ranging in pore size from 500 to 10^5 Å (Phenogel and TSK), was sufficient to separate residual monomer from polymer. The reported polymer molecular weights and distribution values were calculated for the polymer responses only, where residual monomer responses in the chromatogram were excluded.

Cyclohexane, methanol, and pyridine were freshly distilled from calcium hydride. Tetrahydrofuran was freshly distilled from Na/K alloy. Tropic acid, DCC, and DiPC were used as received from Aldrich Chemical Co. The 1:1 PTSA:DMAP complex was synthesized according to the procedure of Moore and Stupp [3]. ^{1}H NMR (δ) (integral): 8.1 (m, 1H), 7.4 (m, 1H), 7.1 (m, 1H), 6.7 (m, 1H), 3.1 (s, 6H), 2.3 (s, 3H). ^{13}C NMR (δ): 158, 140, 129, 126, 107, 40 (N-$\underline{C}H_3$), 22 ($\underline{C}H_3$).

Polymerization Procedure

The temperature, solvent, 1,3-dialkylcarbodiimide, and catalyst system used in each experiment are listed in Table 1.

Dialkylcarbodiimide Activation Method 1

This method was adapted from the procedure of Belcheva [4]. A 50-mL three-necked round-bottom flask equipped with a magnetic stirring bar and an argon inlet was charged with tropic acid (6.8 mmol), PTSA (0.272 mmol), pyridine (1.7 mmol), and 5 mL of a toluene/THF (5:2 v/v) solvent mixture. The mixture was stirred at 50°C for 1 hour and then cooled to 10°C. At this temperature, DCC (8 mmol) was added to the mixture, diluted with 2 mL of the toluene/THF solvent, and the system stirred for 1.5 hours. The mixture was then cooled to −5°C, and stirring was continued for an additional 2.5 hours. The mixture was then filtered, and the solid was washed with dichloromethane. The polymer solution was reduced under vacuum to a white solid which was dissolved in a minimum of dichloromethane and precipitated into a large excess of methanol. The polymer was recovered by centrifugation and freeze dried from benzene under high vacuum ($\leq 10^{-5}$ torr). ^{1}H NMR (δ) (integral): See the Spectroscopic Data Section below. IR (thin film): 3400 (b, O—H stretch), 3000–2900 (s, C—H stretch), 1728 (m, C=O stretch), 1600, 1490 and 1450 (m, s, s, aromatic C=C stretches), 1300–1100 (s, O—C—O ester stretch), 1030 (m) cm^{-1}. Molecular weight $\overline{M}_n$: 1700 (SEC), 1470 (^{13}C NMR). Molecular weight $\overline{M}_w$: 2000 (SEC). Elemental analysis (%): C 71.71; H 5.59; N 0.00 (found); C 73.00, H 5.45, N 0.00 (calculated for repeat unit $C_9H_8O_2$).

Dialkylcarbodiimide Activation Method 2

The following general procedure was used to investigate the polymerization of tropic acid. Specific temperatures, solvents, dialkylcarbodiimides, and catalyst systems used in the experiments are listed in Table 1. A 50-mL three-necked round-bottom flask equipped with a magnetic stirring bar and an argon inlet was flame dried and charged with tropic acid (6.8 mmol), PTSA, pyridine, and 5 mL of a toluene/THF (5:2 v/v) solvent mixture. The mixture was stirred at 50°C for 1 hour and then cooled to the polymerization temperature. The dialkylcarbodiimide was added in one portion, and the system was stirred for 3–5 hours. The mixture was filtered, and the solid was washed with dichloromethane. The solution was concentrated under vacuum, and precipitation was attempted in 50 to 200 mL methanol. If a precipitate formed, the polymer was recovered by centrifugation. If no precipitate formed, the methanol was removed in vacuo to yield solid. SEC analysis was performed on the polymers without further drying or purification. Before NMR analyses, the polymers were freeze dried from benzene or dried in a vacuum ($\leq 10^{-3}$ torr) oven at room temperature overnight.

Dialkylcarbodiimides Activation Method 3

Method 3 differs from Method 2 in that a Schlenk tube equipped with a mechanical stirrer was substituted for a three-necked round-bottom flask equipped with a magnetic stirring bar.

TABLE 1. Results of 1,3-Dicyclohexylcarbodiimide (DCC) and 1,3-Diisopropylcarbodiimide (DiPC) Activated Polymerizations of Tropic Acid[a]

Entry	Solvent[b]	Temperature, °C	PTSA[c]	DMAP[c]	$\overline{M}_w$[d]	$\overline{M}_n$[d]	$\overline{M}_w/\overline{M}_n$[d]	Method[e]	% Yield[f]
1	Toluene/THF[g]	−5 to 10	0.04	—	2000	1700	1.2	1	15
2	Cyclohexane/THF[g,h]	0	0.5	0.5	7500	4400	1.7	2	50
3	Cyclohexane/THF	0	0.5	0.5	4200	2600	1.6	3	30
4	Cyclohexane/THF[i]	0	0.25	0.25	1600	520	3.1	3	0
5	Toluene/THF[g]	50	0.04	—	450	390	1.1	2	0
6	Toluene/THF[g]	25	0.04	—	600	550	1.1	2	0
7	Cyclohexane/THF	−20	0.25	0.25	7500	4300	1.8	3	30
8	Cyclohexane/THF[h]	−20	0.5	0.5	8000	1300	6.0	3	30
9	Cyclohexane/THF[i]	25	0.04	—	1000	880	1.1	2	0
10	Cyclohexane/THF[i]	50	0.04	—	570	500	1.1	2	0
11	Dichloromethane[g,h]	0	0.5	0.5	260	250	1.2	2	0
12	Cyclohexane/THF	0	0.25	0.25	760	530	1.4	2	0

[a]Unless otherwise specified, each experiment used 1.5 mol equivalents of DCC with respect to monomer.
[b]Toluene/THF = cyclohexane/THF = 5 mL/2 mL.
[c]Units are mole equivalents with respect to monomer.
[d]From size exclusion chromatography using polystyrene calibration standards.
[e]Experimental method, see text for details.
[f]Yields of polymer which precipitated in methanol, i.e., if no polymer precipitated, then the yield was recorded as 0.
[g]Pyridine added (0.25 to 0.35 mol equivalents with respect to monomer).
[h]DiPC used in place of DCC (1.5 mol equivalents), and a 1:1 complex of DMAP and PTSA used.
[i]1:1 complex of DMAP and PTSA used.

Spectroscopic Data

Nuclear Magnetic Resonance Data from Dialkylcarbodiimide Model Polymerization

Entry 1, Table 1. ^{1}H NMR (δ) (integral): 7.4–6.8 (0.6111), 4.7–4.0 (0.2412), 4.0–3.6 (0.1331), 0.153–0.018 (0.0146). ^{13}C NMR (δ) (integral): 174 (0.0055), 170 (0.0848), 136–135 (0.0087), 134–133 (0.1070), 130–127 (0.5761), 66–65 (0.0995), 64 (0.0098), 54 (0.0056), 51–50 (0.1031).

Entry 2, Table 1. ^{1}H NMR (δ) (integral): 7.4–6.8 (0.5322), 4.7–4.0 (0.2120), 4.0–3.6 (0.1125), 33.3 (0.0061), 2.5 (0.0081), 1.3–0.97 (0.0340). ^{13}C NMR (δ): 170, 134–133, 130–127, 66–65, 51–50, 23 ($\underline{C}H_3$).

Entry 7, Table 1. ^{1}H NMR (δ) (integral): 7.4–6.8 (0.5874), 4.9–4.0 (0.2344), 4.0–3.6 (0.1161), 2.1–1.6 (ring $C\underline{H}_2$, 0.0914), 1.3–0.97 (0.0719). ^{13}C NMR (δ): 170, 134–133, 130–127, 66–65, 51–50, 42, 25 (ring $\underline{C}H_2$), 24 (ring $\underline{C}H_2$), 22, 21.

Entry 12, Table 1. ^{1}H NMR (δ) (integral): 7.4–6.8 (0.4848), 4.6–4.0 (0.2043), 3.9–3.5 (0.1396), 3.4 (0.0628), 2.0–1.4 (ring $C\underline{H}_2$, 0.0927). ^{13}C NMR (δ): 170, 134, 130–127, 75, 66–65, 51–50, 42, 25 (ring $\underline{C}H_2$), 24 (ring $\underline{C}H_2$).

RESULTS AND DISCUSSION

The poly(tropic acid) produced using the pyridine and PTSA catalyst system of Belcheva [4] has no detectable *N*-acylurea (**5**) end groups as determined by NMR spectroscopy and elemental analysis (see the Experimental Section), and hence the product molecular weight should not to be limited by *N*-acylurea formation (Fig. 2). The limiting factor is more likely a slow polymerization rate which is dependent upon catalyst identity and concentration. Increasing the concentration of PTSA and adding DMAP (equimolar to PTSA) produces poly(tropic acid) with a significantly higher molecular weight as shown in Table 1 (compare Entry 1 to Entries 2, 3, and 4). However, lower molecular weight polymer was achieved with lower concentrations of catalyst (compare Entry 3 vs 4).

The increase in poly(tropic acid) molecular weight with DMAP addition can be explained by the greater catalytic ability of DMAP as compared to pyridine [12]. Both of these bases are thought to undergo nucleophilic attack at the protonated *O*-acylurea (**6**) (Fig. 2) to form acylpyridinium cations (**7**) which upon reaction with alcohol produce ester; however, the electron-donating substituent of DMAP increases its nucleophilicity which makes this analog more effective than pyridine.

While higher molecular weight poly(tropic acid) was achieved with a DMAP catalyst concentration of 0.5 equivalents, spectroscopic analyses of the product polymers detected *N*-acylurea formation. Since strong bases, such as triethylamine, are known to enhance *N*-acylurea formation [10, 13], the greater base strength of DMAP is suspected to be the cause of *N*-acylurea formation.

The increase in *N*-acylurea formation with DMAP can be used to explain the lower polymer molecular weights achieved at DMAP concentrations of 0.25 equivalents. At higher concentrations of DMAP (0.5 equivalents), the increase in the polymerization rate is more significant than the increase in *N*-acylurea formation. At the lower concentrations, the increase in the polymerization rate by DMAP is comparatively less, and *N*-acylurea formation limits molecular weight.

The proportion of *N*-acylurea produced compared to *O*-acylurea decreases with respect to temperature; thus, lower polymerization temperatures can be expected to decrease *N*-acylurea formation and increase molecular weight. In fact, higher molecular weights were achieved at lower polymerization temperatures, particularly when the reaction temperature was lowered below 0°C as shown by the data in Table 1 (compare Entries 1, 5, and 6, compare Entry 2 vs 8, and compare Entry 7 vs 12).

The polarity of the solvent is also known to affect the percentage of *N*-acylurea formation and the rate of reaction in dialkylcarbodiimide-assisted reactions [4, 10, 14]. In this study, higher molecular weight polymers were achieved with cyclohexane/THF than with more polar solvents such as toluene/THF or dichloromethane as outlined in Table 1 (compare Entry 6 vs 9, Entry 5 vs 10, and Entry 2 vs 11 and 13). This trend is consistent with data published by Belcheva [4] in which higher molecular weight polymers were prepared with a benzene/THF solvent pair than with THF alone or with a DMF/dichloromethane solvent mixture.

CONCLUSION

Several trends which lead to higher molecular weight phenyl-substituted aliphatic poly(hydroxy acids) have been established. Dialkylcarbodiimide-activated polyesterification of 3-hydroxy-2-phenylpropionic acid at low temperatures (−20°C), in low polarity solvent pairs (cyclohexane/THF), and using 0.5 equivalents of DMAP and PTSA collectively contribute to produce higher molecular weight poly(tropic acid).

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