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(Trimethylsilyl)ethoxyacetylene as a Dehydrating Agent for Polyanhydride Synthesis

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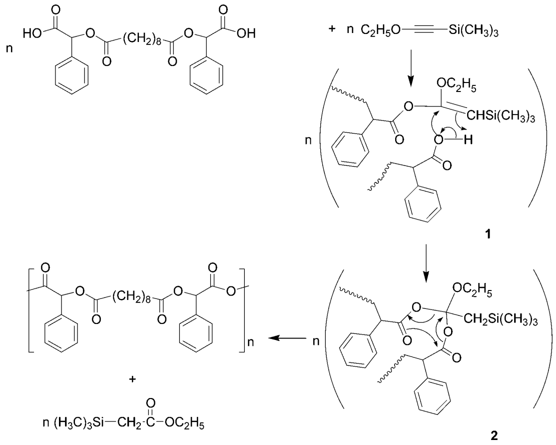
Introduction. In this Communication, we report a low-temperature method for the synthesis of a poly(anhydride−ester) poly[bis[carboxy(phenyl)methyl] sebacate] (PBCS) (Scheme 1) using (trimethylsilyl)ethoxyacetylene as the dehydrating agent. Over the past two decades, there have been extensive studies in the syntheses and applications of polyanhydrides for controlled drug delivery.[1−3] Devices made from polyanhydrides could render a zero-order or constant rate release of incorporated therapeutics, since their erosions could be easily manipulated. The classic method for the synthesis of polyanhydride is through the polycondensation of diacid monomers which are activated by acetylation using acetic anhydride.[4−6] This method was later improved by the use of catalysts to offer products of higher molecular weight.[6] To circumvent the step of prepolymer purification and the side effects of acetic acid during acetylation, ketene was tried to activate diacid monomers instead of acetic anhydride.[7] For poly(adipic anhydride) synthesis, ring-opening polymerizations using different initiators were also successful.[8,9] However, it is the only polyanhydride that was synthesized this way. Most of the aforementioned methods require high temperature for successful polymerization, and a drawback of it is that it could be destructive for monomers and polymers that are heat sensitive. Therefore, two solution polymerization methods that can run at ambient or lower temperatures were investigated, which polymerize a diacid and a diacid chloride with basic catalysts[10] or, alternatively, use dehydrating agents phosgene and diphosgene to work on diacid momomers with basic catalysts.[11] Alkoxyacetylenes have been used for anhydride synthesis,[12,13] of which the trimethylsilyl group substituted derivative (trimethylsilyl)ethoxyacetylene (TMSEA) shows greatly improved stability and reactivity. TMSEA converts many acids to their anhydrides quantitatively under mild conditions. This high reactivity makes TMSEA an ideal candidate as a dehydrating agent for polyanhydride synthesis. We here report our disoveries in poly(anhydride−ester) synthesis using the electrophilic addition−elimination reaction of TMSEA (Scheme 1).

Experimental Section. a. Materials. Chlorotrimethylsilane (≥99%), methyllithium (1.6 M in diethyl ether), pentane (anhydrous, ≥99%), dichloromethane (anhydrous, 99.8%), chloroform (anhydrous, ≥99%), THF (anhydrous, 99.9%), acetonitrile (anhydrous, 99.8%), sebacoyl chloride (technical grade, 92%), and mandelic acid (99%) were purchased from Aldrich. Ethoxyacetylene (technical grade, 50% (w/w) in hexanes) was purchased from Alfa Aesar. Ethyl ether (anhydrous), ethyl acetate, and hexanes were from Mallinckrodt Chemicals. Acetone (extra dry, 99.8%) was from Acros.

b. Characterization. ^{1}H NMR spectra were obtained with a Bruker NMR spectrometer (300 MHz). FTIR spectra were obtained on a Perkin-Elmer Spectrum One FTIR spectrometer with a Perkin-Elmer universal ATR sampling accessory. Polymer molecular weight was measured by gel permeation chromatography (GPC) on two gel columns (Waters, Styragel HR 4E, Styragel HR 5E) in chloroform at 40 °C at a flow rate of 1.0 mL/min. The columns were connected to a Shimadzu LC-10ADVP pump and a RID-10A refractive index detector. The molecular weight and polydispersity index (M_w/M_n) were calculated from the chromatograms using 12 Agilent polystyrene standards ($M_n = 162-1112000$) from Polymer Laboratories Ltd. The results were analyzed using Shimadzu Class-VP 7.2.1 SP1 software.

Scheme 1. Synthesis of PBCS through the Electrophilic Addition−Elimination Reaction of TMSEA



c. Synthesis of (Trimethylsilyl)ethoxyacetylene (TMSEA). TMSEA was synthesized according to a literature reported methods.[14−16] Briefly, ethoxyacetylene solution (75.26 g, 0.54 mol of ethoxyacetylene) was dissolved in 1000 mL of anhydrous ethyl ether at 0 °C. Then methyllithium solution (331.6 mL, 242.73 g, 0.56 mol) was added dropwise in 1 h, and the mixture was stirred at 0 °C for another 30 min. Chlorotrimethylsilane (69.51 mL, 0.55 mol) was then added in 30 min, and the mixture was stirred at room temperature overnight. The solid was filtered and washed with anhydrous ether (100 mL × 3). After ethyl ether was removed under reduced pressure, 250 mL of anhydrous pentane was added, and the additional salts precipitated overnight were filtered. The solution was vacuum-distilled (60 °C, 20 Torr), and the fraction boiling at 28−32 °C was collected (yield, 54.0 g, 75%). Redistillation of the product gave 52.1 g of clear liquid. NMR and IR spectra are in accordance with the literature. ^{1}H NMR (chloroform-*d*): δ 4.13 ppm (q, 2H, $J = 7$ Hz, CH_2), 1.37 ppm (t, 3H, $J = 7$ Hz, CH_3), 0.13 ppm (s, 9H, CH_3). IR: 2960, 2173, and 835 cm^{-1}.

d. Synthesis of Bis[carboxy(phenyl)methyl] Sebacate (BCS). Briefly, 1 equiv of sebacoyl chloride in dry THF was added dropwise to a flask containing 2 equiv of mandelic acid and 2 equiv of pyridine in THF at 0 °C. After the diacid chloride was added in 1 h, the mixture was stirred for an additional 2 h at room temperature. The mixture was then washed with 1 N hydrochloric acid and brine and dried over anhydrous magnesium sulfate. Magnesium sulfate and THF were removed, and the glassy solid was recrystallized in a mixture of ethyl acetate and hexane to give BCS. Yield: 22.7% (white solid). ^{1}H NMR (δ, ppm) (acetone-*d*): δ 7.56 (m, 4H, ArH), 7.42 (m, 6H, ArH), 5.93 (s, 2H, CH), 2.452 (t, 4H, CH_2), 1.67 (m, 4H, CH_2), 1.35

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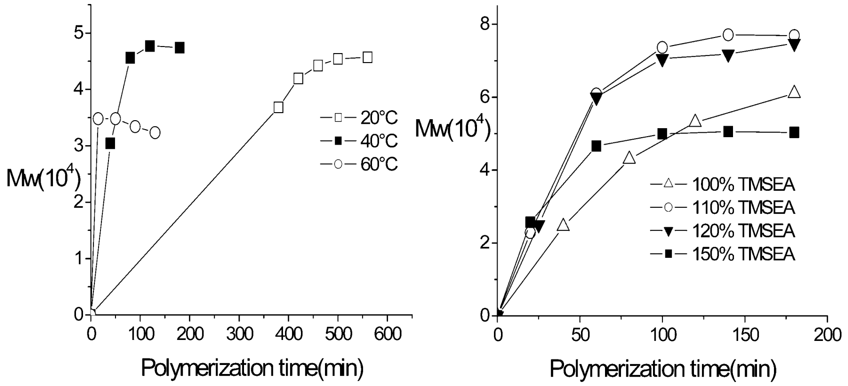

Figure 1. Electrophilic polymerization of BCS using TMSEA as the dehydrating agent. Left: relation between M_w and polymerization temperature, 150% TMSEA, in chloroform. Right: relation between M_w and time at different TMSEA feeding ratios (relative to BCS), in dichloromethane (BCS:dichloromethane = 1:0.4 (mmol:mL)) at 40 °C.

(m, 8H, CH_2). FTIR (cm^{-1}): 3490−2650 (COOH), 1732 (C═O, ester), 1698(C═O, acid). $C_{26}H_{30}O_8$. Molecular weight: 470.51. FAB-MS: $[M + Na]^+$ m/z 493.1, $[M + 2Na - H]^+$ m/z 515.3, $[M + 3Na - 2H]^+$ m/z 537.3. Elemental analysis: calculated, C, 66.37, H, 6.43; found, C, 66.27, H, 6.54. Melting range 139−141 °C.

e. Polymerization of BCS at Different Temperatures. A VWR 4 mL threaded vial (VW60881A-1545) containing a magnetic stirrer bar was purged with dry high-purity argon, and then BCS (0.235 g, 0.5 mmol) and chloroform (0.2 mL) were added to the vial. TMSEA (0.13 mL, 0.76 mmol) was then added, and the vial was sealed with a cap. The vial was kept at 60 °C while stirred for 3 h, and samples were taken with pipets and dissolved in chloroform for GPC measurement. Similarly, the polymerization was carried out at 40 and 20 °C.

f. Polymerization at Different TMSEA Ratios. A VWR 4 mL threaded vial with a magnetic stirrer bar was purged with dry high-purity argon, and then BCS (0.235 g, 0.5 mmol) and dichloromethane (0.2 mL) were added to the vial. TMSEA of a calculated feeding ratio to BCS (100% (0.51 mmol), 110% (0.56 mmol), 120% (0.61 mmol), and 150% (0.76 mmol) molar ratio) was then added, and the vial was kept at 40 °C for polymerization.

g. Polymerization at Different Concentrations. Similar to the procedures mentioned above, the polymerizations were carried out for 3 h at 40 °C in dichloromethane, with a TMSEA to BCS ratio of 110%. BCS to dichloromethane ratios (mmol: mL) of 1:0.4, 1:1, and 1:2 were studied.

h. Polymerization in Different Solvents. A VWR 4 mL threaded vial with a magnetic stirrer bar was purged with dry high-purity argon, and then BCS (0.117 g, 0.25 mmol) and a solvent (acetonitrile, acetone, or tetrahydrofuran) (0.1 mL) were added to the vial. TMSEA was then added with a TMSEA to BCS ratio of 110%, and the polymerization was carried out at 40 °C.

Results and Discussion. For this study, bis[carboxy(phenyl)-methyl] sebacate (BCS) (Scheme 1) was used as the model monomer, and the polymerization went smoothly to yield poly-[bis[carboxy(phenyl)methyl] sebacate] (PBCS) of moderate molecular weight (M_w). We first studied the polymerization in chloroform and dichloromethane at a 1:0.4 (mmol:mL) BCS to solvent ratio, and 150% of TMSEA (molar ratio relative to BCS) was used. The method was effective over a wide range of temperatures (20−60 °C) (Figure 1) to produce colorless polymer products, which is in contrast to the usually brown products of polyanhydrides obtained by classic polycondensation reactions. Spectra of PBCS obtained are shown in Figure 2. The weight-average molecular weight (M_w) (GPC results) of the polymer reached a plateau value in 15 min at 60 °C and in 120 min at 40 °C. The mechanism of anhydride formation from alkoxyacetylenes is believed to comprise three steps,[12,13] namely, monoadduct formation, diadduct formation, and elimination (Scheme 1), and the second addition reaction is believed to be easier than the first addition reaction. As polymerization proceeds, free carboxylic acid end groups will be depleted and leave monoadduct as the only polymer end groups; therefore, no further chain growth is possible, and a plateau value is reached for each polymerization at completion. It appeared that the polymerization reaction was mainly controlled by monomer dissolution, since the polymerization reached plateau quickly after the monomer dissolved at all investigation temperatures. The procedure is so convenient that there is no need of complicated operations; one only needs to seal the monomer and TMSEA in a vial with chloroform or dichloromethane, and the reaction could be conveniently terminated by precipitation from petroleum ether or ethyl ether. The excess of TMSEA and the only byproduct, ethyl trimethylsilylacetate, can be easily removed in vacuo. The best result was obtained in dichloromethane with a BCS to solvent ratio of 1:0.4 (mol:mL), and a usage of 110% TMSEA, giving the highest M_w of 77 000 (M_n = 26 700).

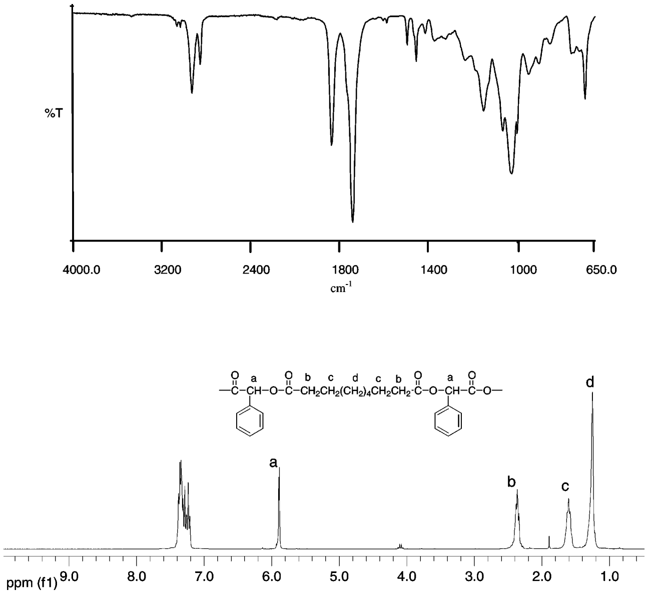

Figure 2. IR and ^{1}H NMR (obtained in $CDCl_3$) spectra of PBCS synthesized in dichloromethane.

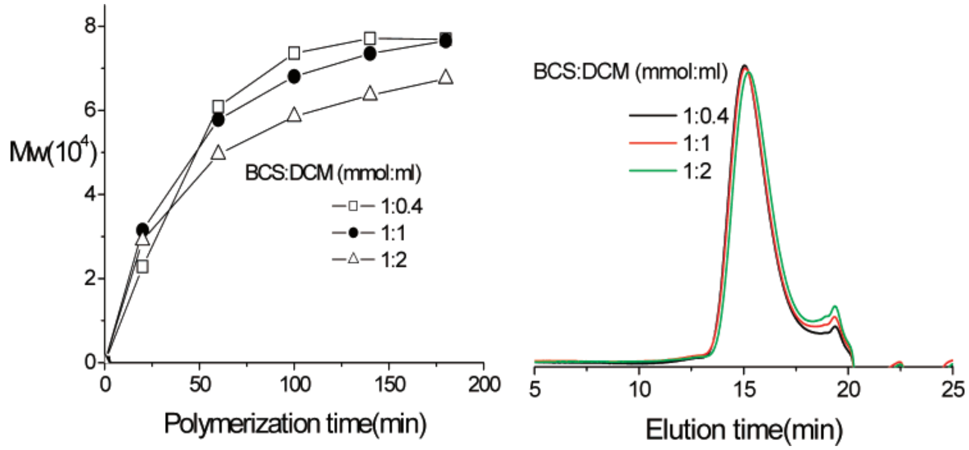

Figure 3. Effects of BCS:dichloromethane (DCM) ratio on electrophilic polymerization. Left: relation between M_w and polymerization time at different monomer to solvent ratios. Right: GPC traces of products obtained.

Table 1. Polymerization Results at 40 °C, with a 1:0.4 (mol:mL) BCS to Solvent Ratio, in Five Hydrogen-Bond Forming Solvents

solvent	polarity index	dielectric constant	π^{*a}	α^a	β^a	M_w (10^4)^b	M_n (10^4)^b	PDI
dichloromethane	3.1	8.93	0.82	0.30	0.00	5.03	1.93	2.61
chloroform	4.1	4.81	0.58	0.44	0.00	4.74	1.88	2.54
ACN	5.8	37.5	0.75	0.19	0.31	2.96	1.00	2.52
acetone	5.1	20.7	0.71	0.08	0.48	2.47	0.69	3.59
THF	4.0	7.58	0.58	0.00	0.58	0.67	0.23	2.94

[a] Hydrogen-bond acidity α and hydrogen-bond basicity β quoted from work of Kamlet et al.[19] [b] GPC measurement. 150% TMSEA in dichloromethane and chloroform, 110% in ACN, acetone, and THF. Polymerization time: 380 min in THF and 180 min in all other solvents.

For alkoxyacetylenes, as mentioned above, it is believed that there are two intermediates formed in the synthesis of anhydrides.[12] The higher electrophilic addition reactivity of intermediate **1**, the monoadduct, is believed to be the key to a continuous chain growth and successful polymerization. If intermediate **1** is, to the opposite, less reactive than TMSEA, low molecular weight molecules with monoadducts as the chain ends will be the predominant product in a system of high (>100%) TMSEA feeding ratios. Our results indicate that, because of the easiness of the second addition, an increase of TMSEA feeding ratio (molar ratio to BCS) from 100% to 150% did not render a dramatic decrease of product molecular weight. However, the TMSEA:BCS ratio does have effects on the molecular weight of the polymer obtained, as shown in Figure 1: 110% TMSEA produced the highest molecular weight. For solution polycondensations, it is desirable to have highest concentration of monomers and intermediates to prevent the formation of cyclic products. Consequently, concentration plays an important role in the electrophilic polymerization, indicated by the different polymerization results at BCS:dichloromethane (mmol:mL) ratio of 1:0.4, 1:1, and 1:2. Less solvent yields product of higher M_w (Figure 3, left) and less oligomer contents, and this is indicated by the reduced intensity of the GPC peak with the elution time of 19 min (Figure 3, right).

We also studied the effects of solvent on the electrophilic polymerization using five solvents: dichloromethane, chloroform, acetonitrile (ACN), acetone, and tetrahydrofuran (THF). It was reported that anhydrides could not be formed in THF,[13] but our IR spectra and GPC traces of the product suggest the formation of a polyanhydride in THF, though of low molecular weight. Similarly, polymerizations in both acetone and acetonitrile only yielded low molecular weight products after 3 h of reaction (Table 1). Polymerizations in dichloromethane and chloroform gave the best results. If we look at the relation between M_w and polymerization time (Figures 1 and 4), it is clear that the reactivity decreases in the order of dichloromethane $\sim$ chloroform $\gg$ ACN $>$ acetone $\gg$ THF. In conventional electrophilic additions of alkynes, increasing solvent polarity can facilitate the addition reactions by stabilizing the cationic addition intermediates. However, in the electrophilic addition reaction of TMSEA and BCS, such a correlation between the polymerization results and solvent polarity or their dielectric constants is not observed (Table 1 and Figure 4, left). Interestingly, there appears to be a correlation between the polymerization reactivities and the hydrogen bond basicities of the investigated solvents. The effects of solvent hydrogen bonding on electrophilic addition reactions of alkynes and alkenes have been documented in the literature.[17,18]

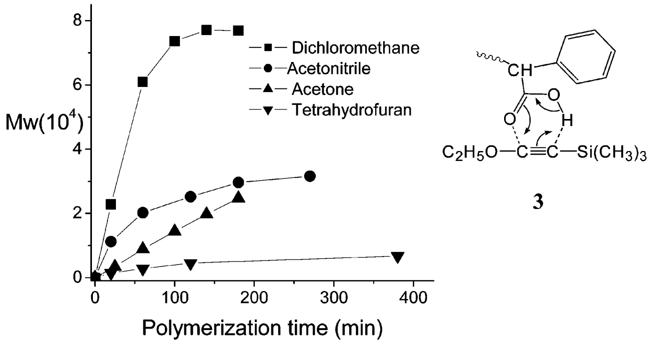

Figure 4. Polymerization in different solvents at 40 °C, with 110% TMSEA and 1:0.4 BCS to solvent ratio (mmol:mL).

To explain our findings, we hypothesize that the electrophilic addition reaction between BCS and TMSEA as well as that between BCS and monoadduct **1** takes a concerted pathway. So the mono- and diadducts **1** and **2** may be formed from nonionic intermediates or transition state complexes, for example, **1** from **3** (Figure 4, right). Since cations and anions are not involved in the formation of **3** and **1**, the charge-stabilizing ability of the solvent is not expected to affect the polymerization significantly. This is in accordance with the observed results (Table 1, Figure 4, left). As is shown, polymerizations in solvents of higher dielectric constants (indicating higher charge stabilizing abilities) did not yield better results. In order to characterize the effects of solvent hydrogen bonding on polymerization, we use the solvent parameter scales that were built by Kamlet et al.[19] to estimate the solvent interacting properties of the solvents (Table 1). Here, the α value of a solvent is the index of its hydrogen bond acidity, β for index of its hydrogen bond basicity, and π^* for index of its dipolarity/polarizability. It appears that there is not a correlation between the dipolarity/polarizability index π^* and the polymerization result, confirming that the charge-stabilizing effects of a solvent is not the key factor. At the mean time, a correlation between the polymerization reactivity and solvent hydrogen bond basicity β could be inferred from the data (Table 1, Figure 4). As is shown, the polymerization went at the lowest rate in THF ($\beta = 0.58$) and gave the lowest molecular weight among all the solvents, while polymerizations in acetone ($\beta = 0.48$) and acetonitrile ($\beta = 0.31$) gave improved results. The best results were obtained in dichloromethane and chloroform, which both have a β value of 0. Our understanding is that the dissolved monomeric diacid BCS and the free carboxylic acid group on the polymer chain may be stabilized through hydrogen-bonding interactions with the hydrogen bond acceptor solvents. As a consequence of this hydrogen bonding, the energy of the bonded free carboxylic acid end group is lowered. The result of this stabilizing effect is the increases of the activation energies of the electrophilic addition reactions of the carboxylic acid to both TMSEA and intermediate **1**. Thus, rates of both the first and the second addition reactions are reduced. It is therefore expected that the activation energies of the reactions are raised further and the polymerization rate lowered more in hydrogen bond acceptor solvents of higher hydrogen bond basicities, indicated by their higher β values. There appeared to be a correlation between solvent hydrogen bond acidity α and the polymerization result, but this correlation is still in doubt, given that the results in chloroform and dichloromethane are very close. Tests in more acidic solvents are needed to confirm this correlation.

Conclusions. In conclusion, electrophilic addition reaction of TMSEA is a mild, effective, and convenient pathway for polyanhydride synthesis. Solvents may play an important role in the reaction by forming hydrogen bonds with the carboxylic acid groups. A good solvent of low hydrogen bond forming ability appears to be the best choice for the synthesis of polyanhydrides using the electrophilic addition−elimination reaction of TMSEA.

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