Biomacromolecules

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Syntheses of Aliphatic Polycarbonates from 2′-Deoxyribonucleosides

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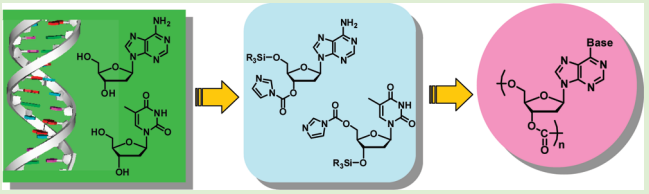
Supporting Information

ABSTRACT: Poly(2′-deoxyadenosine) and poly(thymidine) constructed of carbonate linkages were synthesized by polycondensation between silyl ether and carbonylimidazolide at the 3′- and 5′-positions of the 2′-deoxyribonucleoside monomers. The *N*-benzoyl-2′-deoxyadenosine monomer afforded the corresponding polycarbonate together with the cyclic oligomers. However, the deprotection of the *N*-benzoyl group resulted in the scission of the polymer main chain. Thus, the *N*-unprotected 2′-deoxyadenosine monomers were examined for polycondensation. However, there was involved the undesired reaction between the adenine amino group and the carbonylimidazolide to form the carbamate linkage. In order to exclude this unfavorable reaction, dynamic protection was employed. Strong hydrogen bonding was used in place of the usual covalent bonding for reducing the nucleophilicity of the adenine amino group. Herein, 3′,5′-*O*-diacylthymidines that form the complementary hydrogen bonding with the adenine amino group were added to the polymerization system of the *N*-unprotected 2′-deoxyadenosine monomer. Consequently, although the oligomers (M_n = 1000−1500) were produced, the contents of the carbamate group were greatly reduced. The dynamic protection reagents were easily and quantitatively recovered as the MeOH soluble parts from the polymerization mixtures. In the polycondensation of the thymidine monomer, there tended to be involved another unfavorable reaction of carbonate exchange, which consequently formed the irregular carbonate linkages at not only the 3′-5′ but also the 3′-3′ and 5′-5′ positions. Employing the well-designed monomer suppressed the carbonate exchange reaction to produce poly(thymidine) with the almost regular 3′-5′carbonate linkages.



INTRODUCTION

DNA is a polyphosphate that is composed of 2′-deoxyribonucleosides with the regular 3′-5′ phosphate linkages. We have planned to use 2′-deoxyribonucleosides, which are a kind of renewable resources, as monomer components and to construct novel poly(2′-deoxyribonucleoside)s with various linking groups. The produced biobase polymers are expected to have specific characteristics due to the complementary hydrogen bonding between nucleobase pairs, showing biocompatibility and -degradability. Herein, syntheses of the corresponding polycarbonates from 2′-deoxyadenosine and thymidine have been studied.

There are many known works about oligomers, mainly dimers and trimers, of 2′-deoxyribonucleosides with various linking groups such as carbonate, carbamate, ester, ether, silyl ether, and triazole.[1] They are prepared for the study of antisense molecules. There are many other works using the complementary hydrogen bonding between nucleobase pairs for synthetic polymer materials. Nucleobases are introduced to various polymers as the pendant or terminal groups.[2] There have been disclosed unique organizations of the polymers owing to the complementary hydrogen bonding.

As mentioned above, this article deals with the syntheses of poly(2′-deoxyadenosine) and polythymidine constructed with the regular 3′-5′ carbonate linkages. There are two synthetic ways, ring-opening polymerization and polycondensation, for aliphatic polycarbonate, using chemical reagents or enzymes. Although a green process of enzymatic polymerization would be preferable especially for polymer synthesis from renewable resources, it can be applied to limited monomers for the preparation of polycarbonate.[3] A literature survey has actually revealed that carbohydrate-based polycarbonates are prepared by ring-opening polymerization as well as polycondensation using chemical reagents.[4] Our project needs the regular formation of the intermolecular 3′-5′ carbonate linkage between the ribose rings. To our first expectation, regio-selective ring-opening polymerization could satisfy our demand together with controlling the molecular weight. However, unfortunately, the corresponding cyclic monomer was not obtained from 2′-deoxyadenosine. Thus, the second choice was polycondensation of an AB type monomer, which should produce the regioregular connection. In contrast, chemical or enzymatic polycondensation between AA and BB type monomers, typically the combination of phosgene or dialkyl carbonate with diol for polycarbonate, is unfavorable for the regioselective formation of asymmetric carbonate linkages. Thus, we decided to employ the literature method for polycarbonate synthesis.[5] Therein, cyclohexane-1,4-diol is transformed to the AB monomer having silyl ether and carbonylimidazolide and subjected to polycondensation, which is conducted by desilylation with the added fluorine anion and

Received: November 8, 2010
Revised: March 2, 2011
Published: March 05, 2011

subsequent attack of the generated alkoxide anion to the active carbonyl group. This methodology is expected to be applicable to our project; the corresponding monomers can be prepared by the individual transformation of the 3′- and 5′-hydroxyl groups of 2′-deoxyadenosine and thymidine ribose rings to a combination of the silyl ether and the carbonylimidazolide.

EXPERIMENTAL SECTION

Measurements. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE-200FT-NMR and -600FT-NMR spectrometers in $CDCl_3$ (0.03 v/v% TMS as the internal standard), DMSO-d_6 (the signals due to the residual protons and the carbon were used for the standards), and DMF (1 v/v% TMS as the internal standard). The IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer by KBr pellet and ATR methods. The MALDI-TOF mass spectra were recorded on a SHIMADZU/KRATOS AXIMA-CFR plus spectrometer (matrix, 2-(4-hydroxyphenylazo)benzoic acid; cast solvent, 1,1,1,3,3,3-hexafluoro-2-propanol). Gel permeation chromatography (GPC) was conducted on tandem columns of TOSOH TSKgel ALPHA5000 and ALPHA3000 (eluent, DMF with KBr (0.5 g/L); calibration, polystyrene standards). Silica gel 60N (Kanto Kagaku) was used for column chromatography.

Materials. DMF, CH_3CN, and Et_3N used for the monomer syntheses and the polymerizations were dried over CaH_2 and distilled under N_2. Other reagents were used as received. The preparation of starting compounds for monomer syntheses is described in Supporting Information.

3′-*O*-(Imidazol-1-yl)carbonyl-5′-*O*-triisopropylsilyl-*N*-benzoyl-2′-deoxyadenosine (1). To a solution of 5′-*O*-triisopropylsilyl-*N*-benzoyl-2′-deoxyadenosine (1.27 g, 2.47 mmol) in dry toluene (13 mL) were added a catalytic amount (50−80 mg) of powdery KOH and subsequently carbonyl diimidazole (616 mg, 3.80 mmol) under N_2. TLC analyses (AcOEt/MeOH = 9/1) suggested that the starting material (R_f = 0.67) faded out and quantitatively gave the product (R_f = 0.60) for 1.5 h at r.t. The reaction mixture was diluted with toluene (50 mL) and washed successively with two portions of water and brine. Drying the organic layer over $MgSO_4$ and excluding toluene in vacuo gave 3′-*O*-(imidazol-1-yl)carbonyl-5′-*O*-triisopropylsilyl-*N*-benzoyl-2′-deoxyadenosine (1.45 g, 97%). No impurity was detected by TLC as well as ^{1}H NMR spectroscopy; therefore, the product was used for polymerization without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.01 (s, 1H), 8.82 (s, 1H), 8.34 (s, 1H), 8.21 (s, 1H), 8.03 (s, 1H), 7.66−7.50 (m, 3H), 7.49 (s, 1H), 7.14 (s, 1H), 6.63 (dd, 1H, J = 8.5 Hz, J = 5.8 Hz), 5.82 (d-like, 1H, J = 5.6 Hz), 4.45 (s-like, 1H), 4.09 (d-like, 2H, J = 3.2 Hz), 3.03 (m, 1H), 2.88 (m, 1H), 1.08−1.26 (m, 21H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.0, 152.7, 151.6, 149.8, 148.1, 141.0, 137.2, 133.6, 132.8, 131.1, 128.8, 128.0, 123.5, 117.1, 85.4, 84.3, 79.4, 63.6, 38.5, 18.0, 11.9. IR (ATR, cm^{-1}) 3146, 3008, 2941, 2865, 1769, 1690, 1581, 1513, 1393, 1283, 1127, 994, 755.

Polycondensation of *N*-Protected Adenosine Monomer 1. *With CsF (No. 1, Table 1).* CsF (0.53 g, 3.5 mmol) in a test tube was heated with a heat gun under vacuum for 5 min. Into the test tube under N_2 were added a magnetic stirrer chip, dry DMF (1.3 mL), and **1** (401 mg, 0.66 mmol). The reaction mixture became a white gel and hardly stirred. After 20 h at r.t., it was poured into water (50 mL) to give a white precipitate, which was isolated by centrifugation and successively washed with water (50 mL × 4), methanol (50 mL × 2), and diethyl ether. Drying under vacuum gave a white powdery polymer (176 mg, 70%yield).

With TBAT (No. 2, Table 1). Tetrabutylammonium triphenyldifluorosilicate (TBAT) (440 mg, 0.81 mmol) was added to the solution of **1** (405 mg, 0.67 mmol) in dry DMF (1.3 mL) under N_2 and stirred for 20 h at r.t. The reaction mixture was poured into methanol (50 mL), and the white precipitate was isolated by centrifugation. Successive wash with methanol (50 mL × 4) and diethyl ether was followed by drying under vacuum to give a white powdery polymer (198 mg, 78% yield).

^{1}H NMR (DMSO-d_6, 200 MHz, ppm) δ 11.16 (1H), 8.78−8.65 (2H), 8.01 (2H), 7.57 (3H), 6.53 (1H), 5.53−5.43 (1H), 4.56−4.29 (3H), 3.30 (1H, overlapped with H_2O peak), 2.70 (1H). ^{13}C NMR (DMSO-d_6, 50 MHz, ppm) δ 165.8, 153.6, 152.0, 151.8, 150.5, 143.3, 133.4, 132.5, 128.5, 125.9, 84.1, 81.3, 78.2, 67.2, 35.4. IR (ATR, cm^{-1}) 1748, 1695, 1608, 1581, 1454, 1246, 1073, 708.

3′-*O*-(Imidazol-1-yl)carbonyl-5′-*O*-(*t*-butyl)dimethylsilyl-*N*-monomethoxytrityl-2′-deoxyadenosine (2). Carbonyl diimidazole (0.78 mg, 4.88 mmol) was dissolved into dry THF (3 mL) under N_2 and stirred with a catalytic amount (50−80 mg) of powdery KOH at 0 °C. Then, the dry THF solution (9 mL) of 5′-*O*-(*t*-butyl)dimethylsilyl-*N*-MMTr-2′-deoxyadenosine (2.01 mg, 3.15 mmol) was added dropwise. The reaction was monitored by TLC, which detected no spot due to the starting material (R_f = 0.61, EtOAc) after 40 min at 0 °C. The reaction mixture was diluted with EtOAc, washed with three portions of water, and dried over $MgSO_4$. Vacuum drying gave a white solid of 3′-*O*-(imidazol-1-yl)carbonyl-5′-*O*-TBDMS-*N*-MMTr-2′-deoxyadenosine (1.88 g, 81%yield). No impurity was detected by TLC (R_f = 0.51, EtOAc) as well as ^{1}H NMR spectroscopy; therefore, the product was used for polymerization without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) δ 8.17 (s, 1H), 8.09 (s,1H), 8.06 (s, 1H), 7.44 (s, 1H), 7.35−7.23 (m, 12H), 7.11 (s, 1H), 6.93 (s, 1H), 6.79 (d, 2H, J = 8.8 Hz), 6.51 (dd, 1H, J = 8.7, 5.9 Hz), 5.68 (d-like, 1H, J = 5.4 Hz), 4.39 (m, 1H), 3.97 (d-like, 2H, J = 3.0 Hz), 3.78 (s, 3H), 2.87 (m, 2H), 0.92 (s, 9H), 0.12 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm) δ 158.4, 154.2, 152.4, 148.6, 148.2, 145.2, 137.8, 137.2, 137.1, 131.1, 130.3, 128.9, 127.9, 126.9, 121.2, 117.1, 113.2, 85.1, 84.2, 79.8, 71.1, 63.5, 55.2, 38.6, 26.0, 18.4, −5.3, −5.5. IR (KBr, cm^{-1}) 3413, 2954, 2929, 2856, 1763, 1605, 1471, 1400, 1290, 1250, 1179, 1002, 835.

Polycondensation of *N*-Protected Adenosine Monomer 2. Monomer **2** was polymerized by the same procedure as monomer **1**, giving the corresponding polycarbonate. ^{1}H NMR (DMSO-d_6, 200 MHz, ppm) δ 8.38 (1H), 7.90 (1H), 7.41−7.20 (13H), 6.82 (2H), 6.34 (1H), 5.35 (1H), 4.30 (3H), 3.70 (3H), 3.25−2.60 (2H, overlapped with H_2O and solvent peaks). IR (KBr, cm^{-1}) 3411, 1754, 1605, 1510, 1471, 1252, 1182, 1034, 706.

3′-*O*-(Imidazol-1-yl)carbonyl-5′-*O*-triisopropylsilyl-2′-deoxyadenosine (3). Carbonyl diimidazole (569 mg, 3.51 mmol) was dissolved into dry THF (4 mL) under N_2 and stirred with a catalytic amount (50−80 mg) of powdery KOH at 0 °C. Then, the dry THF solution (6 mL) of 5′-*O*-TIPS-2′-deoxyadenosine (1.01 g, 2.48 mmol) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C, was diluted with EtOAc, washed with three portions of water, and dried over $MgSO_4$. The organic phase was concentrated, and hexane was slowly added under ice cooling to give a white precipitate, which was collected by filtration and dried in vacuo. No impurity was detected by TLC (R_f = 0.28, EtOAc/MeOH = 9:1) as well as ^{1}H NMR spectroscopy; therefore, the obtained white powder of 3′-*O*-(imidazol-1-yl)carbonyl-5′-*O*-TIPS-2′-deoxyadenosine (1.15 g, 92%yield) was used for polymerization without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) δ 8.36 (s, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 7.46 (s, 1H), 7.26 (s, 1H), 6.55 (dd, 1H, J = 8.5, 5.8 Hz), 5.80 (d-like, 1H, J = 5.7 Hz), 5.62 (s, 2H), 4.42 (m, 1H), 4.08 (d-like, 2H, J = 3.3 Hz), 2.99 (m,1H), 2.83 (m, 1H), 1.11−1.08 (m, 21H). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm) δ 155.8, 153.3, 149.7, 148.2, 138.5, 137.3, 131.2, 120.0, 117.2, 85.3, 84.2, 79.6, 63.7, 38.6, 18.1, 12.0. IR (ATR, cm^{-1}) 3321, 3194, 2942, 2866, 1780, 1631, 1596, 1287, 1237, 1170, 1051, 1005, 648.

3′-*O*-(Imidazol-1-yl)carbonyl-5′-*O*-(*t*-butyl)dimethylsilyl-2′-deoxyadenosine (4). Carbonyl diimidazole (2.2 g, 13.6 mmol)

was dissolved into dry THF (15 mL) under N_2 and stirred with a catalytic amount (50−80 mg) of powdery KOH at 0 °C. Then, the dry THF solution (25 mL) of 5′-*O*-TBDMS-2′-deoxyadenosine (3.53 g, 9.64 mmol) was added dropwise, and the mixture was stirred at 0 °C. The reaction was monitored by TLC, which showed no spot due to the starting material (R_f = 0.41, EtOAc/MeOH = 9:1) after 7 h. Thus, the reaction mixture was diluted with EtOAc, washed with three portions of water, and dried over $MgSO_4$. The residue obtained by evaporation was dissolved into EtOAc, and hexane was slowly added under ice cooling to give a white precipitate, which was collected by filtration and dried in vacuo. The obtained white powder of 3′-*O*-(imidazol-1-yl)carbonyl-5′-*O*-TBDMS-2′-deoxyadenosine (3.37 g, 76%yield) had no impurity detected by TLC (R_f = 0.35, EtOAc/MeOH = 9:1) as well as ^{1}H NMR spectroscopy; therefore, it was used for polymerization without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) δ 8.36 (s, 1H), 8.19 (s, 1H), 8.18 (s, 1H) 7.46 (s, 1H), 7.12 (s, 1H), 6.57 (dd, 1H, J = 7.9, 6.4 Hz), 5.88 (s, 2H), 5.70 (m, 1H), 4.42 (m, 1H), 3.99 (d-like, 2H, J = 3.0 Hz), 2.89 (m, 2H), 0.93 (s, 9H), 0.14 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm) δ 156.0, 152.9, 149.3, 147.9, 138.0, 137.0, 130.8, 119.6, 116.9, 84.9, 84.1, 79.6, 63.3, 38.5, 25.7, 18.2, −5.6, −5.7. IR (KBr, cm^{-1}) 2926, 2859, 1765, 1602, 1397, 1322, 1282, 1241, 1124, 1005, 836, 772, 650

Polycondensation of 2′-Deoxyadenosine Monomer 4 with Dynamic Protection. The typical procedures are as follows. To the DMF (2.8 mL) solution of 3′-*O*-(imidazol-1-yl)carbonyl-5′-*O*-TBDMS-2′-deoxyadenosine (328 mg, 0.71 mmol) and 3′,5′-*O*-dipivaroyl thymidine (886 mg, 2.16 mmol) was added $(n\text{-Bu})_4NPh_3SiF_2$ (TBAT) (462 mg, 0.86 mmol) under N_2. The mixture was stirred for 22.5 h and then poured into MeOH to give a white precipitate, which was collected by centrifugation and washed with four portions of MeOH and one portion of Et_2O. Drying the precipitate in vacuo gave a white powder of the objective polycarbonate (172.9 mg, 86%yield, M_n = 1,000, M_w/M_n = 2.64 (GPC; DMF+LiBr 0.5 g/L, 40 °C, PSt std)). The MeOH- and Et_2O-soluble parts were concentrated and subjected to silica gel column chromatography (EtOAc/hexane = 1:2, R_f = 0.15) to recover 3′,5′-*O*-dipivaroylthymidine (842 mg, 95%yield). ^{1}H NMR (DMSO-d_6, 200 MHz, ppm) δ 8.31 (1H), 8.15 (1H), 7.31 (2H), 6.43−6.36 (1H), 5.38 (1H), 4.44−4.35 (3H), 3.25 (1H, overlapped with H_2O peak), 2.60 (1H, overlapped with DMSO peak), 0.80 (end group, Si(*t*-Bu)), −0.01 (end group, $SiMe_2$). ^{13}C NMR (DMSO-d_6, 200 MHz, ppm) δ 156.2, 153.6, 152.7, 149.2, 139.8, 119.4, 83.8, 81.2, 78.2, 67.4, 35.0, 25.7 (end group, $Si(C(CH_3))Me_2$), 17.9 (end group, $Si(C(CH_3))Me_2$), −5.55 (end group, $Si(t\text{-Bu})(CH_3)_2$). IR (KBr, cm^{-1}) 3334, 3186, 1753, 1640, 1599, 1475, 1245, 1080, 932, 786, 651.

3′-*O*-(Imidazol-1-yl)carbonyl-5′-*O*-triisopropylsilylthymidine (8). Carbonyl diimidazole (492 mg, 3.0 mmol) was dissolved into dry THF (5 mL) under N_2 and stirred with a catalytic amount (50−80 mg) of powdery KOH at 0 °C. Then, the dry THF solution (5 mL) of 5′-*O*-TIPSthymidine (1.01 g, 2.53 mmol) was added dropwise, and the mixture was stirred at 0 °C. The reaction was monitored by TLC (EtOAc/hexane = 9:1), which showed no spot due to the starting material (R_f = 0.46) after 0.5 h. Thus, the addition of water and NaCl to the reaction mixture was followed by the extraction with three potions of EtOAc. The organic phase combined was washed with three portions of water and dried over $MgSO_4$. The residue obtained by evaporation was dissolved into EtOAc, and hexane was slowly added under ice cooling to give a white precipitate, which was collected by filtration and dried in vacuo. The obtained white powder of 3′-*O*-(imidazol-1-yl)carbonyl-5′-*O*-TIPSthymidine (923 mg, 74%yield) had no impurity detected by TLC (R_f = 0.30, EtOAc/MeOH = 9:1) as well as ^{1}H NMR spectroscopy; therefore, it was used for polymerization without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) δ 9.54 (s, 1H), 8.21 (s, 1H), 7.49 (s, 1H), 7.46 (s, 1H), 7.11 (s, 1H), 6.43 (dd, 1H, J = 9.0, 5.1 Hz), 5.63 (d-like, 1H, J = 5.7 Hz), 4.31 (s-like, 1H), 4.08 (m, 2H), 2.67 (m, 1H), 2.29 (m, 1H), 1.93 (s, 3H), 1.14−1.12 (m, 21H). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm) δ 163.8, 150.6, 148.4, 137.3, 134.6, 131.1, 117.2, 111.7, 85.1, 84.5, 79.3, 63.8, 38.1, 18.1, 12.5, 12.0. IR (KBr, cm^{-1}) 2945, 2867, 1764, 1691, 1469, 1401, 1320, 1279, 1242, 1127, 1003, 883, 769, 650.

3′-*O*-(Imidazol-1-yl)carbonyl-5′-*O*-(*t*-butyl)dimethylsilylthymidine (9). To the solution of 5′-*O*-TBDMSthymidine (1.38 g, 3.87 mmol) in dry THF (13 mL) were successively added a catalytic amount (50−80 mg) of KOH powder and carbonyl diimidazole (0.95 g, 5.9 mmol). The reaction was monitored by TLC, which showed no spot due to the starting material (R_f = 0.45, EtOAc) after 2 h at r.t. Thus, the reaction mixture was diluted with EtOAc, washed with three portions of water, and dried over $MgSO_4$. The residue obtained by evaporation was dissolved into toluene, and hexane was slowly added to give a white precipitate, which was collected by filtration and dried in vacuo. The obtained white powder of 3′-*O*-(imidazol-1-yl)carbonyl-5′-*O*-TBDMSthymidine (1.64 g, 94%yield) had no impurity detected by TLC (R_f = 0.30, EtOAc) as well as ^{1}H NMR spectroscopy; therefore, it was used for polymerization without further purification. The melting point was measured for the sample recrystallized from toluene with hexane (mp; 177−179 °C). ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) δ 8.53 (br, 1H), 8.18 (s, 1H), 7.53 (s, 1H), 7.44 (s, 1H), 7.12 (s, 1H), 6.42 (dd, 1H, J = 9.3, 5.3 Hz), 5.51 (d-like, 1H. J = 5.8 Hz), 4.32 (s-like, 1H), 3.99 (d-like, 2H, J = 1.7 Hz), 2.65 (m, 1H), 2.26 (m, 1H), 1.95 (s, 3H), 0.95 (s, 9H), 0.17 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm) δ 164.0, 150.7, 148.3, 137.3, 134.5, 130.9, 117.1, 111.5, 84.9, 84.7, 79.6, 63.5, 37.9, 25.9, 18.3, 12.5, −5.4, −5.5. IR (KBr, cm^{-1}) 3296, 3097, 2950, 2929, 2857, 1743, 1706, 1688, 1469, 1407, 1323, 1276, 1262, 1179, 1126, 1006, 835, 783.

3′-*O*-(*t*-Butyl)dimethylsilyl-5′-*O*-(imidazol-1-yl)carbonylthymidine (10). Carbonyl diimidazole (1.3 g, 8.0 mmol) was dissolved into dry THF (10 mL) under N_2 and stirred with a catalytic amount (50−80 mg) of powdery KOH at 0 °C. Then, the dry THF solution (20 mL) of 3′-*O*-TBDMSthymidine (1.85 g, 5.2 mmol) was added dropwise, and the mixture was stirred at 0 °C. The reaction was monitored by TLC (EtOAc), which showed no spot due to the starting material (R_f = 0.47) after 1 h. Thus, the reaction mixture was diluted with EtOAc, washed with three portions of water, and dried over $MgSO_4$. Vacuum drying gave a white solid of 3′-*O*-TBDMS-5′-*O*-(imidazol-1-yl)carbonylthymidine (1.97, 84%yield), which had no impurity detected by TLC (R_f = 0.30, EtOAc/MeOH = 9:1) as well as ^{1}H NMR spectroscopy and whose recrystallization was impossible to achieve. Accordingly, it was used for polymerization without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) δ 8.54 (br, 1H), 8.18 (s, 1H), 7.43 (s, 1H), 7.11 (s, 1H), 7.07 (s, 1H), 6.12 (t-like, 1H, J = 6.6 Hz), 4.70−4.41 (m, 3H), 4.12 (m, 1H), 2.43−2.20 (m, 2H), 1.87 (s, 3H), 0.90 (s, 9H), 0.10 (s, 6H). ^{13}C NMR ($CDCl_3$, 200 MHz, ppm) δ 164.2, 150.3, 148.3, 137.1, 135.9, 130.6, 116.9, 111.1, 86.4, 83.6, 71.3, 66.6, 40.0, 25.5, 17.7, 12.3, −4.8, −5.1. IR (KBr, cm^{-1}) 2954, 2931, 2858, 1768, 1693, 1472, 1404, 1292, 1241, 1104, 1005, 836, 780.

Polycondensation of Thymidine Monomers Representatively Using 10. *With TBAT (No. 9, Table 5).* To a dry DMF (1.36 mL) solution of **10** (307 mg, 0.68 mmol) under N_2 was added TBAT (0.48 g, 0.88 mmol). The mixture was stirred for 43.5 h at r.t. and then poured into water. The white precipitate generated was collected by centrifugation and successively washed with five portions of MeOH and one portion of diethyl ether. Vacuum drying gave a white powder of the polymer (95 mg, 52%).

With CsF (No. 12, Table 5). CsF (0.49 g, 3.3 mmol) in a test tube was heated with a heat gun under vacuum for 5 min. Into the test tube under N_2 were added a magnetic stirrer chip and dry DMF (1.3 mL). Then, **10** (401 mg, 0.66 mmol) was added at 0 °C, and the mixture was stirred for 20 h at this temperature. The reaction mixture became a white gel and hardly stirred during that period. It was poured into

Scheme 1. Polycondensation of *N*-Bz-2′-Deoxyadenosine Monomer 1

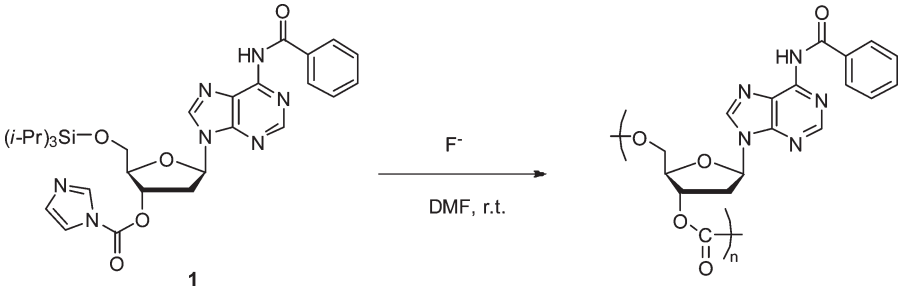


Table 1. Polycondensation of *N*-Bz-2′-Deoxyadenosine Monomer 1 at r.t.

	fluoride anion					
no.	source	eq.	monomer conc. (M)	time (h)	yield[a] (%)	molecular weight[b] M_p
1	CsF	5.3	0.51	20	70	3,800, 14,600
2	TBAT	1.2	0.51	20	78	2,000, 5,700
3	TBAT	5.2	0.25	65	81	1,500, 7,300

[a] A MeOH-insoluble part. [b] M_p: the molecular weight at the peak top of the GPC profile (DMF+LiBr 0.5 g/L, 40 °C, PSt std.). TBAT: $(n\text{-Bu})_4NPh_3SiF_2$

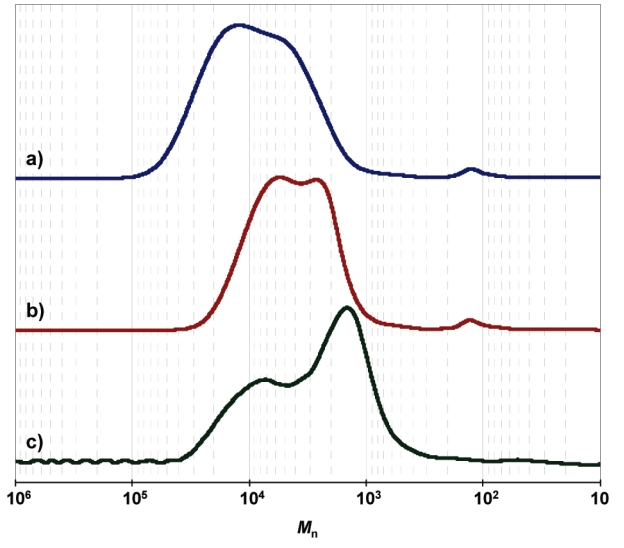


Figure 1. GPC profiles of *N*-Bz-2′-deoxyadenosine polycarbonates: no. 1 (a), no. 2 (b), and no. 3 (c) in Table 1 (DMF+LiBr 0.5 g/L, 40 °C, PSt std.).

water (50 mL) to give a white precipitate, which was collected by centrifugation and successively washed with two portions of water and three portions of MeOH, and one portion of Et_2O. Drying under vacuum gave a white powdery polymer (169 mg, 96%yield).

^{1}H NMR (DMSO-d_6, 200 MHz, ppm) δ 11.34 (1H), 7.52−7.48 (1H), 6.19 (1H), 5.21 (1H), 4.39 and 4.30 (3H), 2.44 (2H), 1.80 (3H), 0.85 and 0.08 (Si(*t*-Bu)Me_2 end group). ^{13}C NMR (DMSO-d_6, 50 MHz, ppm) δ 163.7, 153.6, 150.5, 136.0, 110.2, 84.3, 80.7, 77.8, 67.5, 35.5, 12.2. IR (KBr, cm^{-1}) 1753, 1687, 1473, 1406, 1249, 1104, 958, 891, 784.

RESULTS AND DISCUSSION

Polymerization of *N*-Protected Adenosine Monomers. The amino group of adenine was speculated to disturb the polymerization by the nucleophilic attack to the carbonylimidazolide; therefore, *N*-protected adenosine monomers were examined. In order to get preliminary information, the most popular protective group, the *N*-benzoyl, was employed for the first monomer, **1**, consequently found to be polymerized with the aid of CsF or $(n\text{-Bu})_4NPh_3SiF_2$ (TBAT) in DMF at r.t. (Scheme 1 and Table 1). CsF is insoluble in DMF but more efficiently promoted the polymerization than DMF-soluble TBAT, affording the higher molecular weight product.

The product polymers showed bimodal GPC profiles (Figure 1), which were consistent with MALDI-TOF mass spectra (Figure 2). As observed in Figure 2, there are two peak series with the regular intervals due to the objective repeating unit, and they are assignable to the cyclic and linear polycarbonates, respectively. The ^{1}H and ^{13}C NMR and IR spectra also supported the polymer structure (Supporting Information, Figures S1−S4).

Although we supposed that the deprotection of the *N*-benzoyl group without affecting the carbonate linkage would be difficult, it was examined. Usual deprotection conditions, the treatment with 28% NH_3 aq. at 50 °C, resulted in complete deprotection but simultaneously the frequent cleavage of the carbonate linkage.

Accordingly, the monomethoxytrityl group, which could be excluded under milder conditions, was employed for *N*-protection. The corresponding adenosine monomer **2** was found to be polymerized under the same conditions with **1** (Supporting Information, Scheme S1 and Table S1), however, giving the lower molecular weight oligomer (M_n = 1700−1900) probably due to the steric hindrance of the monomethoxytrityl group. ^{1}H NMR, IR, and MALDI-TOF mass spectra supported the polymer structure (Supporting Information, Figures S5−S7). The MALDI-TOF mass spectra suggested the production of the linear and cyclic oligomers, showing the predominant formation of the cyclic trimer.

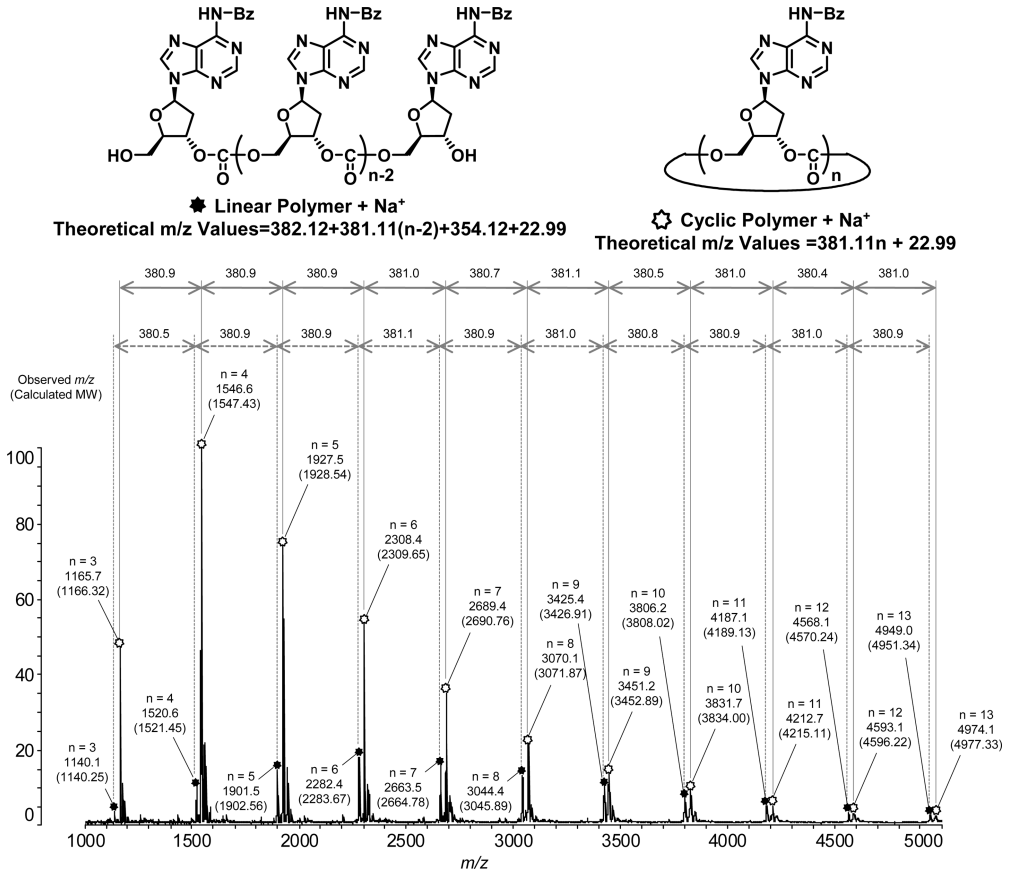


Figure 2. MALDI-TOF mass spectrum of *N*-Bz-2′-deoxyadenosine polycarbonate (no. 3, Table 1). 2-(4-Hydroxyphenylazo)benzoic acid as a matrix.

Table 2. Polycondensation of *N*-Unprotected 2′-Deoxyadenosine Monomers 3 and 4 at r.t.

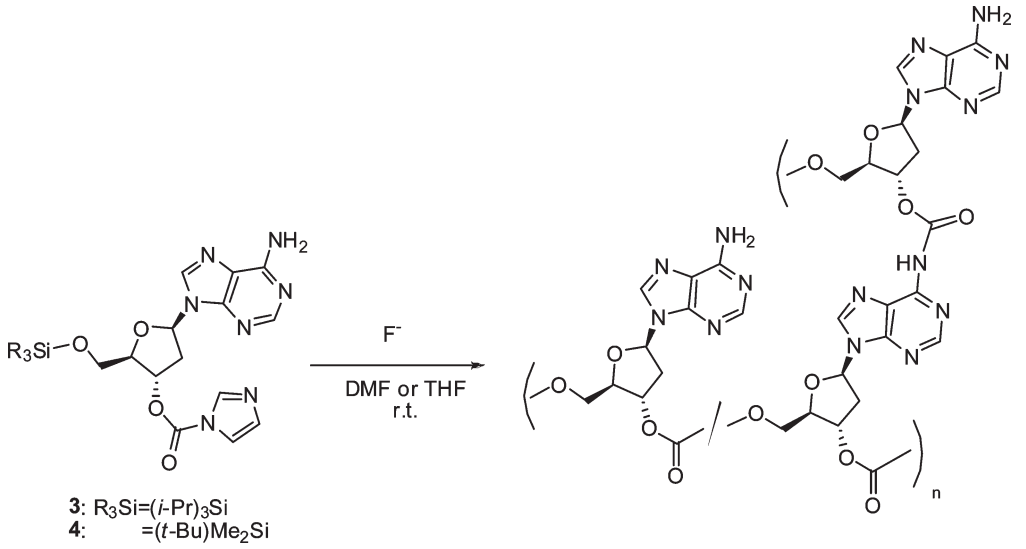
		fluoride anion						molecular weight[b]		
no.	monomer	source	eq.	solv.	monomer conc. (M)	time (h)	yield[a] (%)	M_n	M_w/M_n	carbamate content[c] (%)
1	**3**		–	DMF	0.50	30.5				
3	**3**	TBAT	1.2	DMF	0.50	20	quant.	4,200	3.56	38
4	**3**	TBAT	1.2	THF	0.50	22	70	3,400	6.15	35
5	**4**	CsF	5.0	DMF	0.50	18.5	–	DMF-insoluble		–
6	**4**	TBAT	1.2	THF	0.25	23	–	DMF-insoluble		–
7	**4**	TBAT	1.3	DMF	0.25	20	quant.	2,900	2.18	32
8	**4**	TBAT	1.3	DMF	0.50	24	quant.	3,400	3.89	37

[a] A MeOH-insoluble part. [b] GPC (DMF+LiBr 0.5 g/L, 40 °C, PSt std.). [c] Calculated from ^{1}H NMR spectra.

Polymerization of *N*-Unprotected 2′-Deoxyadenosine Monomers. During the preparation of *N*-protected monomers **1** and **2**, we found them contaminated with a trace amount of the corresponding *N*-unprotected compounds. This means that the carbonylimidazolide group is unexpectedly tolerant to the adenine amino group. Thus, we were encouraged to prepare the *N*-unprotected 2′-deoxyadenosine monomers and succeeded in getting two monomers **3** and **4**.

Table 2 summarizes the polymerization results of monomers **3** and **4**. The control reaction without the fluoride anion showed that the monomers were stable in DMF at r.t. (no. 1), while the addition of the fluoride anion promoted polymerization. However, the product polymers were found to be composed of not only the carbonate but also the carbamate linkages, the latter of which were provided by the reaction between the carbonylimidazolide and the adenine amino groups, giving as a result the hyperbranched structure (Scheme 2). This undesired reaction was not suppressed in all runs of Table 2; the relative contents of the carbamate unit were evaluated to be 32−38% by the ^{1}H NMR spectra (Figure 3). This finding means that the tolerance of the carbonylimidazolide group to the adenine amino group is lost in the presence of the fluoride anion, which presumably increases the nucleophilicity of the adenine amino group through F^--HN hydrogen bonding in addition to the activation of silyl ether. There is another possibility that the carbamate linkage could be formed by the reaction of the adenine amino group with the

Scheme 2. Polycondensation of *N*-Unprotected 2′-Deoxyadenosine Monomers 3 and 4



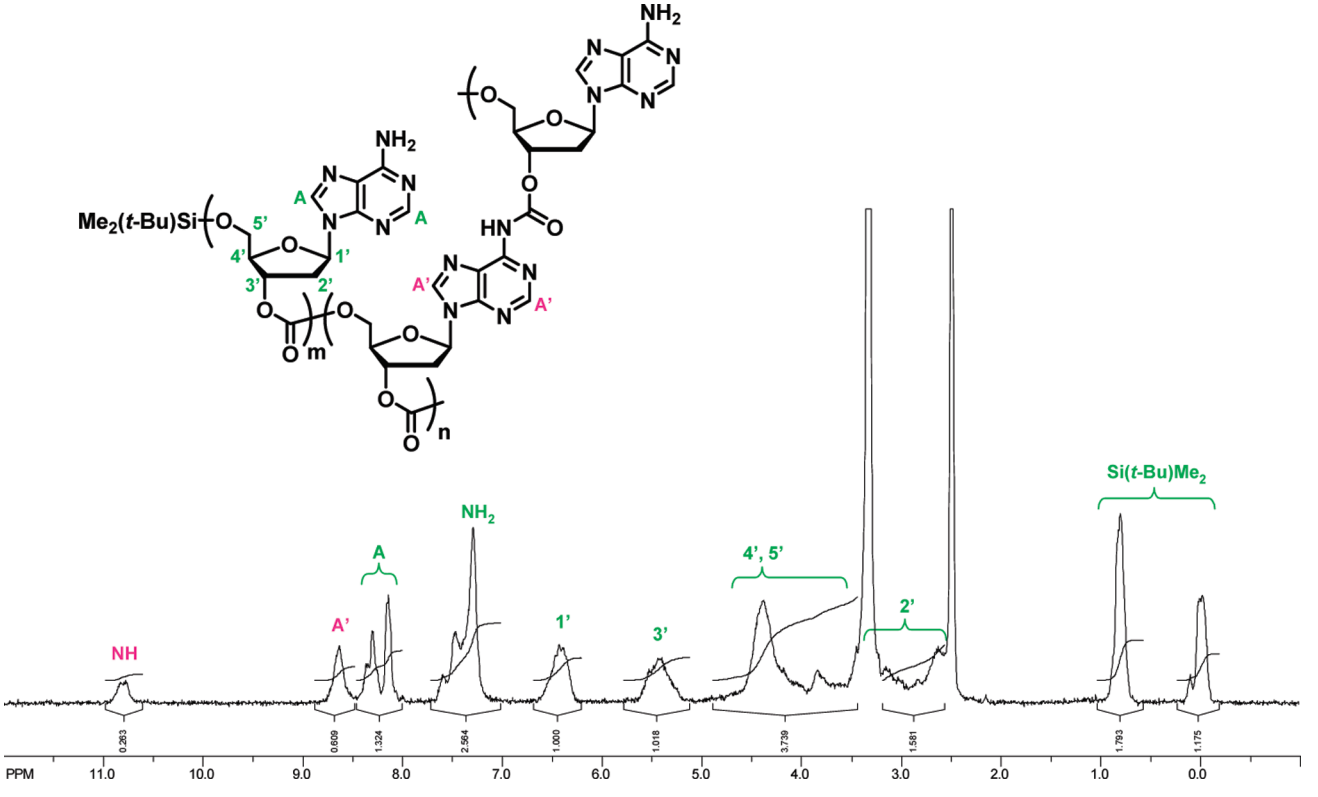


Figure 3. ^{1}H NMR spectrum (DMSO-d_6, 200 MHz) of polymer from **4** (no. 7, Table 2).

carbonate linkage, but it was excluded by the control experiment. No formation of the carbamate linkage was observed when oligo(2′-deoxyadenosine carbonate) prepared from **4** with dynamic protection (see the next section) was treated with TBAT (1.2 equiv) in DMF at r.t. for 23 h similarly to the polymerization conditions. Thus, it is concluded that the adenine amino group activated with the fluoride anion has the ability to react with the carbonylimidazolide group but not with the carbonate group for forming the carbamate linkage.

In order to exclude the undesired carbamate formation, we came up with the idea of dynamic protection, where strong hydrogen bonding would work to reduce the nucleophilic reactivity of the amino group instead of the usual covalent bonding protection. ^{1}H NMR spectroscopy revealed that the complementary H-bonding between the adenine and the thymine moieties is formed even in DMF. Mixing monomer **3** with 3′,5′-*O*-diacylthymidine caused both the adenine and thymine NH proton signals to undergo a downfield shift depending on their concentration

Table 3. ^{1}H NMR Study of H-Bonding Interaction between the 2′-Deoxyadenosine TBDMS Monomer 4 with 3′,5′-*O*-Diacylthymidines

			down field shift (ppm)[a]	
hydrogen bonding pair	adenosine (M)	thymidine (M)	adenine NH_2	thymine NH
2′-deoxyadenosine TBDMS monomer **4** + 3′,5′-*O*-diacetylthymidine **5**	0.25	0.25	0.03	0.34
	0.25	0.75	0.07	0.31
	0.50	0.50	0.02	0.58
	0.50	1.00	0.04	0.55
	0.50	1.50	0.08	0.50
2′-deoxyadenosine TBDMS monomer **4** + 3′,5′-*O*-dipivaroylthymidine **6**	0.25	0.25	0.02	0.35
	0.25	0.75	0.07	0.33

[a] ^{1}H NMR spectroscopy in DMF at 25 °C.

Scheme 3. Polymerization of 2′-Deoxyadenosine TBDMS Monomer 4 with Dynamic Protection

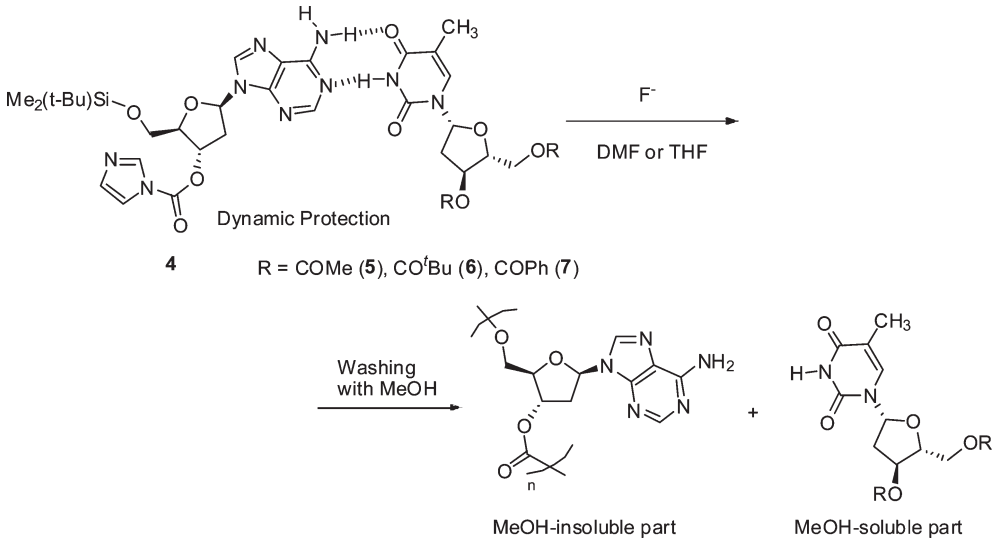


Table 4. Polycondensation of 2′-Deoxyadenosine TBDMS Monomer 4 with Dynamic Protection

	fluoride anion		dynamic protection						molecular weight[b]		
no.	source	eq.	additive	eq.	solv.	conc. of **4** (M)	time (h)	yield[a] (%)	M_n	M_w/M_n	carbamatecontent[c] (%)
1	TBAT	1.2	**5**	1.6	DMF	0.25	20	88	1,500	1.57	7.2
2	TBAT	1.3	**5**	3.0	DMF	0.25	21	72	1,100	1.51	2.3
3	TBAT	1.4	**5**	3.0	DMF	0.25	67	81	1,300	1.60	1.7
4	TBAT	1.2	**5**	3.0	DMF	0.50	24	105	1,300	1.58	5.4
5	CsF	5.0	**5**	3.0	DMF	0.19	43.5	89	1,000	2.26	14.5
6	TBAT	1.2	**6**	3.0	DMF	0.25	21	92	1,000	2.07	1.1
7	TBAT	1.3	**6**	3.0	DMF	0.50	21	96	1,200	2.00	0
8	TBAT	1.2	**7**	3.0	DMF	0.125	24	80	1,000	1.89	0
9	TBAT	1.2	**5**	3.1	THF	0.24	20	89	1,000	1.63	3.8
10	TBAT	1.2	**6**	1.0	THF	1.00	16.5	85	1,400	1.94	6.8
11	TBAT	1.2	**6**	1.0	THF	0.50	16.5	98	1,400	1.98	3.6
12	TBAT	1.2	Thymine	1.0	DMF	0.25	20	85	1,200	1.89	6.8
13	TBAT	1.2	Thymine	3.1	DMF	0.25	20	90	1,100	1.50	1.7

[a] A MeOH-insoluble part. [b] GPC (DMF+LiBr 0.5 g/L, 40 °C, PSt std.). [c] Calculated from ^{1}H NMR spectra.

dx.doi.org/10.1021/bm101328j |*Biomacromolecules* 2011, 12, 1449–1459

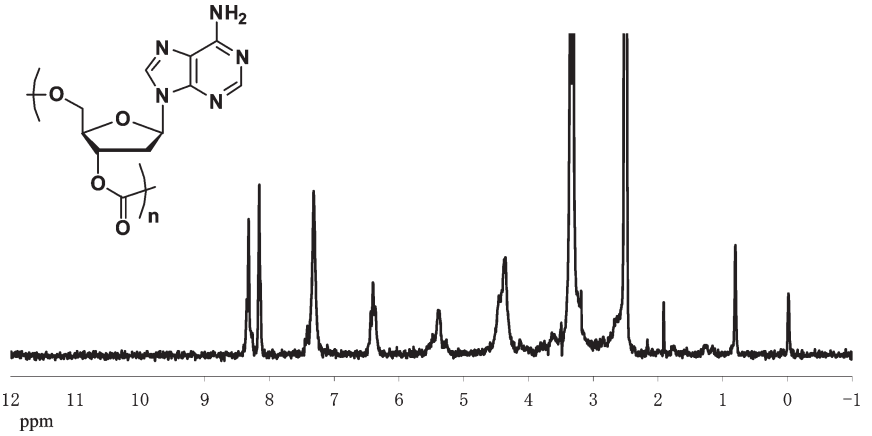
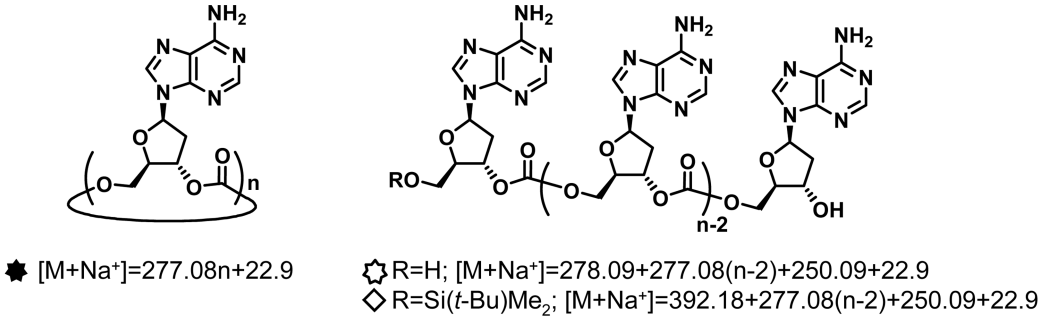


Figure 4. ^{1}H NMR spectrum (DMSO-d_6, 200 MHz) of the oligomer from **4** with dynamic protection (no. 7, Table 4).



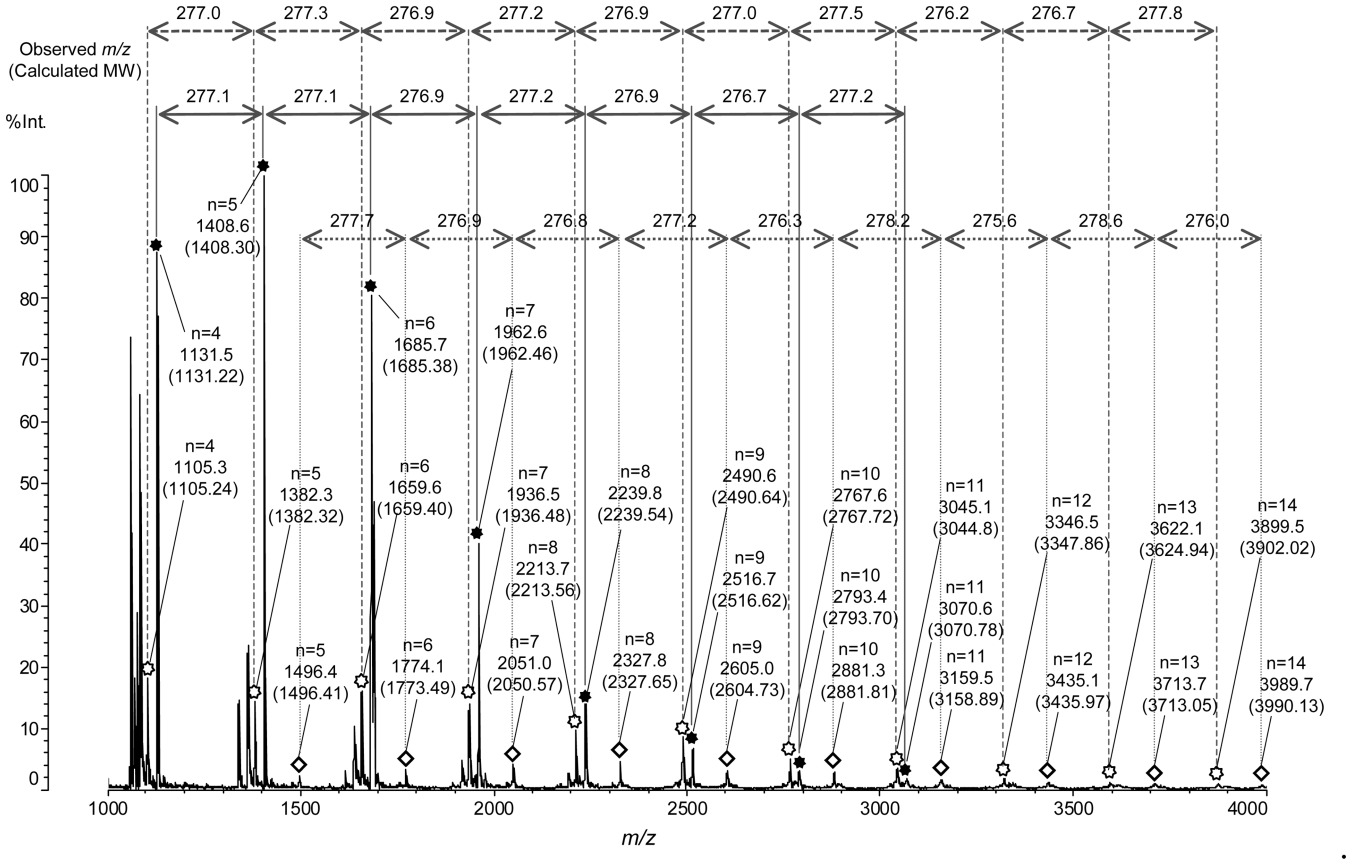
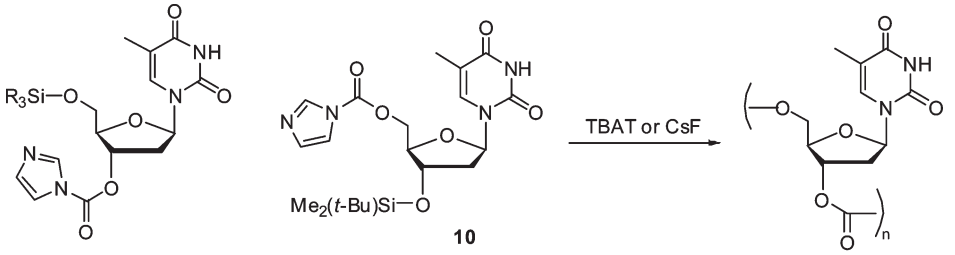


Figure 5. MALDI-TOF mass spectrum of 2′-deoxyadenosine oligocarbonate (no. 7, Table 4). 2-(4-Hydroxyphenylazo)benzoic acid as a matrix.

Scheme 4. Polymerization of Thymidine Monomers



8: $SiR_3 = Si(i\text{-}Pr)_3$
9: $SiR_3 = Si(t\text{-}Bu)Me_2$
10

Table 5. Polycondensation of Thymidine Monomers

		fluoride anion							molecular weight[b]		
no.	monomer	source	eq.	solv.	monomer conc. (M)	temp. (°C)	time (h)	yield[a] (%)	M_n	M_w/M_n	proportion of 3′-5′ carbonate linkage[c] (%)
1	**8**	TBAT	1.2	DMF	0.50	40	24	85	3,300	1.95	44
2		TBAT	1.2	DMF	0.50	40	72	61	2,100	1.44	–
3		CsF	4.1	DMF	0.58	r.t.	23	66	4,700	1.86	74
4	**9**	TBAT	1.2	DMF	0.50	r.t.	70	75	2,700	1.72	–
5		TBAT	1.2	THF	0.25	r.t.	94.5	94	4,000	2.37	52
6		CsF	5.0	DMF	0.50	r.t.	43.5	90	4,000	2.12	66
7		CsF	4.2	DMF	0.48	0	21.5	93	3,100	2.35	78
8		CsF	5.1	DMF	0.48	0	44.5	98	3,200	2.32	71
9	**10**	TBAT	1.3	DMF	0.50	r.t.	43.5	52	1,700	1.40	70
10		CsF	5.1	DMF	0.25	r.t.	46.5	91	3,900	2.13	75
11		CsF	5.0	DMF	0.50	r.t.	42	87	3,900	1.92	78
12		CsF	4.9	DMF	0.51	0	20	96	3,900	2.03	>90

[a] A MeOH-insoluble part. [b] GPC (DMF+LiBr 0.5 g/L, 40 °C, PSt std.). [c] Calculated from ^{13}C NMR spectra.

(Table 3 and Supporting Information, Figure S8). The shift values of the adenine amino proton signal were small, as compared with those of the thymine NH proton signal, but increased with increasing relative concentrations of the thymidine derivative, showing the complementary H-bonding interaction.

The polycondensation of 2′-deoxyadenosine TBDMS monomer **4** was conducted in the presence of 3′,5′-*O*-diacylthymidine **5**, **6**, or **7** (Scheme 3 and Table 4). As compared with the polymerization without them (Table 2), the formation of the carbamate linkage was extremely reduced. The efficiency of the dynamic protection was increased by using a three times excess amount of 3′,5′-*O*-diacylthymidine with TBAT as the fluoride anion source. The representative ^1H NMR spectrum (Figure 4) shows no signal due to the adenine protons that form the carbamate linkage, which are observed in Figure 3. However, the obtained product was the low molecular weight oligomer; therefore, improvements in reaction conditions were investigated. However, unfortunately, the longer reaction time (no. 3) and the higher monomer concentration (no. 4) hardly increased the molecular weight. Using THF in place of DMF as the solvent gave almost comparable results (no. 9–11). Thymine, which could have a smaller steric hindrance than 3′,5′-*O*-diacylthymidine, was also found to act as the dynamic protection reagent (no. 12–13), but the product was also the oligomer. The complementary H bonding interaction causes

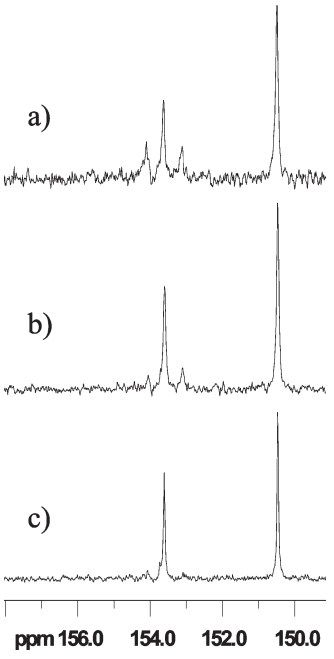
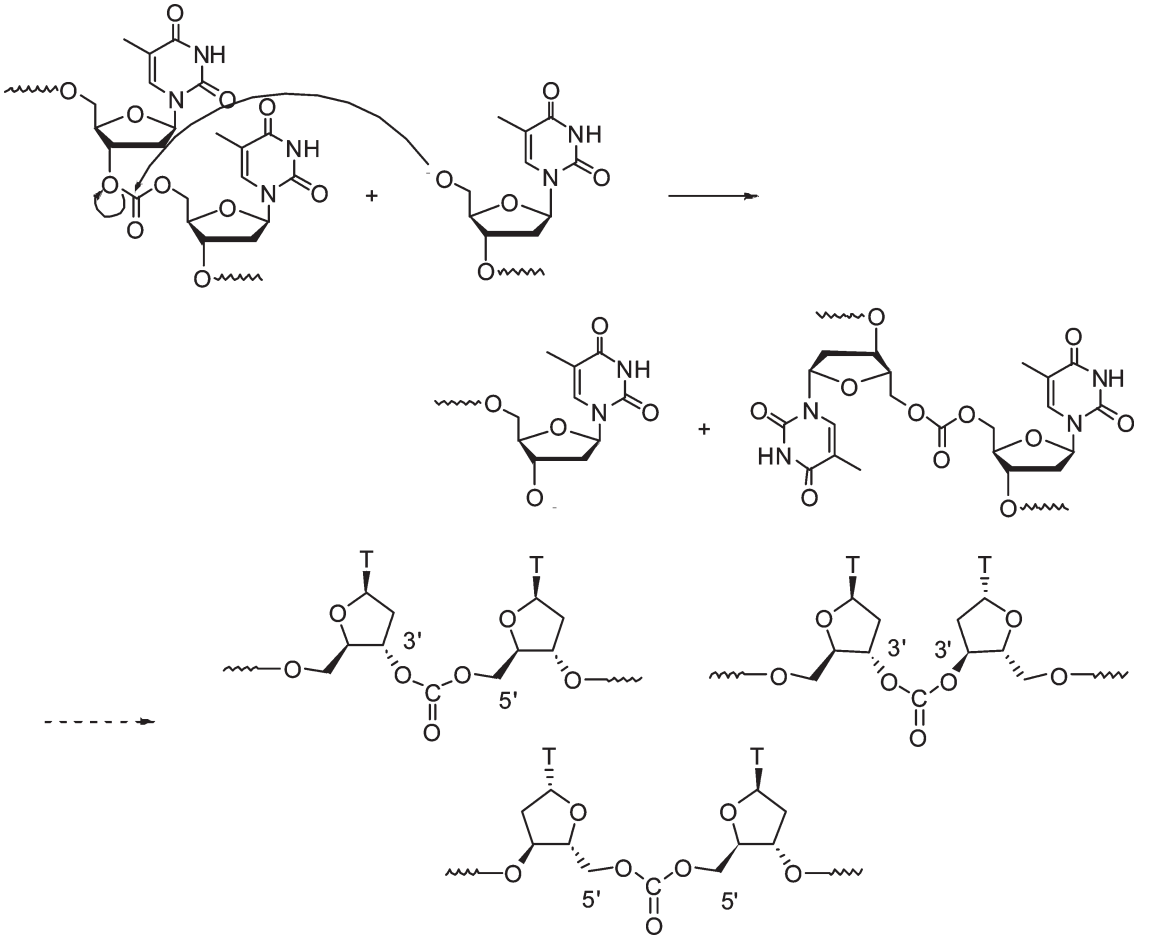


Figure 6. ^{13}C NMR spectra of the product polymers from thymidine monomers: nos. 1 (a), 7 (b), and 12 (c) in Table 5.

Scheme 5. Carbonate Exchange Reaction during Polymerization



this low reactivity by steric hindrance, probably affecting the conformation of the ribose ring causing it to be unfavorable for polycondensation. Although this drawback should be overcome, the dynamic protection is a convenient methodology. Actually, the protection reagent, 3′,5′-*O*-diacylthymidine, was easily and almost quantitatively recovered as the MeOH-soluble part from the reaction mixture. MALDI-TOF mass, ^{13}C NMR, and IR spectra further supported the identification of the product (Figure 5 and Supporting Information, Figures S9 and S10); mass spectrometry suggested that linear and cyclic oligocarbonates were produced.

Polymerization of Thymidine Monomers. Since thymidine has no nucleophilic amino group, no problem was expected for the monomer synthesis as well as the polymerization (Scheme 4). Thymidine TIPS monomer **8** was found to require heating at 40 °C for the polymerization in the presence of TBAT, while CsF conducted the polymerization even at r.t. (no. 1−3, Table 5). Comparing **8** with the corresponding adenosine monomers **1** and **3**, which were polymerized at r.t. with the aid of TBAT (Tables 1, 2, and 4), suggests that the nucleobase would indirectly affect the reactivity of the polymerization sites on the ribose ring.

The product polymers from **8**, contrary to expectations, contained irregular structures, as revealed by the ^{13}C NMR spectra (Figure 6a). There were observed three carbonyl carbon signals, which were assigned to the 3′-3′, 3′-5′, and 5′-5′ carbonate linkages by comparison with the model dimers (Supporting Information). This finding is ascribable to the unfavorable side reaction of the carbonate exchange. Therein the alkoxide anion attacks not the carbonylimidazolide for the chain elongation but the carbonate linkage in the polymer main chain, regenerating another alkoxide anion (Scheme 5). The frequent carbonate exchange reactions consequently cause the carbonate connection to lose regioregularity.

In order to exclude this unfavorable reaction, monomer **9** was examined since the *t*-BuMe_2Si group of **9** was expected to decrease the polymerization temperature due to the higher reactivity compared to that of the (*i*-Pr)$_3$Si group of **8**. Actually, TBAT and CsF conducted the polycondensation of **9** at r.t. and 0 °C, respectively (no. 4−8, Table 5). However, the carbonate exchange reaction was comparably involved in producing the irregular carbonate linkages (Figure 6b). Accordingly, we designed monomer **10**, whose polymerization sites are mutually replaced in contrast with **8** and **9**. In monomer **10**, the silyl ether group at the 3′-position generates more sterically hindered alkoxide, while the carbonylimidazolide group at the 5′-position has the higher reactivity due to the smaller steric hindrance. These factors would be favorable for suppressing the reaction of the alkoxide with the carbonate linkage of the polymer main chain and relatively promoting that with the

carbonylimidazolide group. The polymerization results of **10** met our expectations (no. 9−12, Table 5). The contents of the 3′-5′ carbonate linkage were increased; especially, the polymer produced at 0 °C using CsF (no. 12) hardly showed the ^{13}C NMR signals due to the 3′-3′ and 5′-5′ carbonate carbonyl carbons (Figure 6c). This regio regular polycarbonate from thymidine was identified also by ^{1}H NMR, IR, and MALDI-TOF mass spectra (Supporting Information, Figures S11, S12, and S13), suggesting the involvement of both the linear and the cyclic polymers similarly to the polycarbonates from adenine monomers **1** and **4**.

CONCLUSIONS

As mentioned above, we have synthesized the oligomers and polymers from 2′-deoxyadenosine and thymidine with the 3′-5′ regular carbonate linkages. However, further investigations including not only chemical but also enzymatic reaction systems are necessary for increasing the molecular weights of the product polymers and extending this project to another pair, i.e., 2′-deoxy-guanosine and -cytidine, as well as other linking groups. The additional interest coming next is the study of supramolecular interaction between two kinds of polycarbonates from the complementary 2′-deoxynucleosides.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures to prepare the starting materials for the monomer syntheses, figures showing ^{1}H and ^{13}C NMR and IR spectra of the polycarbonate from **1**, partial ^{13}C NMR spectra of the model dimers, ^{1}H NMR, IR, and MALDI-TOF mass spectra of the polycarbonate from **2**, ^{1}H NMR spectra for the observation of hydrogen bonding interaction between **4** and **5**, ^{13}C NMR and IR spectra of the polycarbonate from **4** with the dynamic protection, ^{13}C NMR and MALDI-TOF mass spectra of the polycarbonate from **10**, and a scheme and a table of the polycondensation of monomer **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

We thank Yuki Gosei Kogyo Co., Ltd. for gifting us 2′-deoxyadenosine, thymidine, and triisopropylsilyl chloride. We appreciate the contribution of Mr. Tomoaki Goto, a member of our laboratory, for performing the control experiment to prove no reaction of the adenine amino group with the carbonate linkage.

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