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Synthesis and Properties of DNA Oligomers Containing 2′-Deoxynucleoside *N*-Oxide Derivatives

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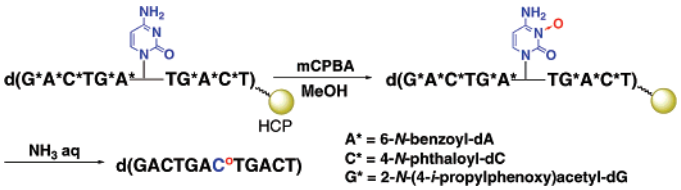

Cytosine and adenine *N*-oxide derivatives have long been known as products resulting from the oxidative damage of DNA by peroxides such as hydrogen peroxide. Although the synthesis and properties of 2′-deoxynucleoside *N*-oxide derivatives have been well described, little has been reported about the chemical and biochemical behavior of initially formed DNA oligomers containing these *N*-oxide bases. In this study, we established a convenient method for the solid-phase synthesis of oligodeoxynucleotides incorporating 2′-deoxycytidine *N*-oxide (dC^O) or 2′-deoxyadenosine *N*-oxide (dA^O) by using the postsynthetic oxidation of N-protected DNA oligomers except for the target dC or dA site with *m*-CPBA in MeOH in a highly selective manner. In this strategy, the benzoyl, phthaloyl, and (4-isopropylphenoxy)-acetyl groups proved to serve as base protecting groups to avoid oxidation of adenine, cytosine, and guanine, respectively, at the unmodified sites.

Introduction

DNA base oxidation has been recognized as a major cause of genetic mutation. Oxidative DNA damage is associated with cancer, aging, and genetic diseases.[1,2] Reactive oxygen species such as hydroxyl radical, peroxyl radical, and hydrogen peroxide have been known to oxidize DNA bases. Free radicals such as hydroxyl radical reacts with pyrimidine and purine bases to give many oxidation products.[3−7] For example, oxidatively modified structures such as thymine glycol, uracil glycol, and 8-oxoguanine have been found. These modifications have been found to block the chain elongation by DNA polymerases or to lead mutations.[8−11]

On the other hand, nonradical processes are also important in understanding the mechanism of oxidative DNA damage. Hydrogen peroxide is a major nonradical species in living cells produced by a series of metabolic processes of a nonreactive superoxide anion.[12,13] Adenine N^1-oxide is a specific product derived from the adenine residue of DNA upon treatment with H_2O_2 under nonradical conditions,[14] and it has been detected in cellular DNA after exposure to nonlethal concentrations of H_2O_2 (Figure 1).[15,16] Brown et al. previously reported strong growth inhibitory activity of adenosine N^1-oxide and AMP N^1-

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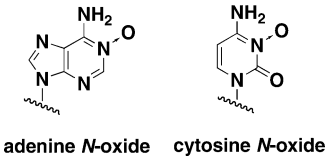


FIGURE 1. Adenine and cytosine *N*-oxide derivatives.

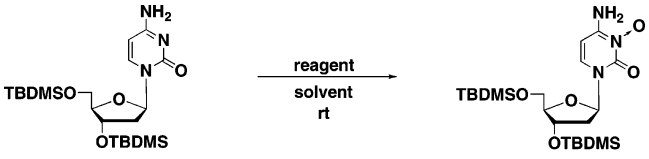
oxide in mouse sarcoma 180 cell.[17] 2′-Deoxycytidine N^3-oxide[18−21] was also considered as a principle component of the oxidation products of DNA upon treatment with hydrogen peroxide, although this modified species has not been detected from modified 2′-deoxynucleosides induced by oxidative DNA damage. There is a possibility that these 2′-deoxynucleoside *N*-oxides are mutagenic in DNA replication like the well-known 8-oxoguanine.[22]

The chemical synthesis of cytosine and adenine *N*-oxides have been reported previously in a number of laboratories. Adenine underwent preferential N^1-oxidation with 30% aqueous hydrogen peroxide in acetic acid.[23] Monoperoxyphthalic acid has been used to convert cytosine and cytidine into the corresponding N^3-oxides.[18] *m*-Chloroperoxybenzoic acid (*m*-CPBA), a commercially available stable peroxide, has also been used for the synthesis of adenosine and cytidine *N*-oxide derivatives.[19−21] Although many studies concerning the formation and properties of nucleoside *N*-oxide derivatives have been conducted until date, little attention has been paid to oligodeoxynucleotides containing cytosine or adenine *N*-oxide. If oligomers incorporating a nucleoside *N*-oxide at an appropriate position could be synthesized, it is possible to clarify its biological behavior. With this background in mind, we studied the synthesis of DNA oligomers containing a 2′-deoxynucleoside *N*-oxide.

Results and Discussion

For the *N*-oxidation of deoxynucleosides, several methods using peroxides have been reported. To find the most favorable conditions for the *N*-oxidation, reactions of 3′,5′-bis(*tert*-butyldimethylsilyl)-2′-deoxycytidine **1** with several peroxides were examined in aqueous and nonaqueous solvents, as shown in Table 1. *t*-BuOOH is known as a widely used reagent for the oxidation of phosphite triester intermediates in DNA synthesis.[24−26] It turned out that this reagent was completely inactive toward the cytosine base for 24 h (entries 1 and 2). When compound **1** was treated with 30% hydrogen peroxide and trifluoroacetic anhydride,[27] the *N*-oxide derivative **2** was formed in a low yield of 31% (entry 3). The combined use of urea hydrogen peroxide (UHP) and trifluoroacetic anhydride (TFAA) was effective for the conversion of pyridine derivatives into their *N*-oxide derivatives.[27] However, the *N*-oxide **2** could only be obtained in moderate yields (entries 5−8). In contrast, when mCPBA was used in MeOH, the *N*-oxidation proceeded more smoothly (entries 9−12). The use of 3 equiv of *m*-CPBA in MeOH gave the best result. Under similar conditions, 3′,5′-*O*-bis(*tert*-butyldimethylsilyl)-2′-deoxyadenosine **3** could be oxidized to give the *N*-oxide derivative **4** in 92% yield, as shown in Scheme 1.

TABLE 1. Synthesis of 2′-Deoxycytidine *N*-Oxide Derivative 2 by Treatment of 1 with Several Peroxides[a]

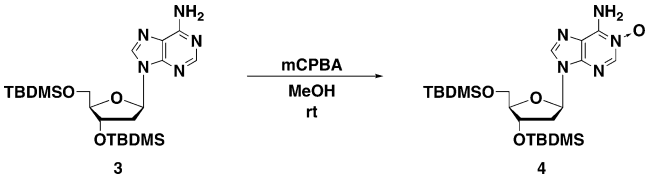


1 2

entry	reagent (equiv)	solvent	time (h)	yield (%)
1	*t*-BuOOH (1)	CH_3CN	24	no reaction
2	*t*-BuOOH (1)	CH_2Cl_2	24	no reaction
3	30% H_2O_2 (2), TFAA (2)	CH_3CN	24	31
4	30% H_2O_2 (2), TFAA (2)	CH_2Cl_2	24	19
5	UHP (2), TFAA (2)	THF	4	39
6	UHP (2), TFAA (2)	CH_3CN	4	33
7	UHP (2), TFAA (2)	CH_2Cl_2	12	14
8	UHP (2), TFAA (2)	MeOH	24	10
9	*m*-CPBA (1)	CH_3CN	24	48
10	*m*-CPBA (1)	CH_2Cl_2	24	55
11	*m*-CPBA (1)	MeOH	24	71
12	*m*-CPBA (3)	MeOH	90 min	89

[a] UHP = ureahydrogenperoxide; TFAA = trifluoroacetic anhydride.

SCHEME 1. Synthesis of 2′-Deoxyadenosine *N*-Oxide Derivative 4 by Treatment of 3 with *m*-CPBA



3 4

We attempted to synthesize the phosphoramidite unit **8** of 2′-deoxycytidine *N*-oxide for the synthesis of oligodeoxynucleotides containing dC^O in the usual manner (Scheme 2). Reaction of **2** with dibutylformamide dimethyl acetal in MeOH gave the 4-*N*-protected product **5** in 99% yield. During this reaction, the *N*-oxide function was stable. The usual tritylation of **5** with DMTrCl gave the 5′-masked product **7** in 71% yield. However, the last phosphitylation of **7** with chloro(2-cyanoethoxy)-(diisopropylamino)phosphine resulted in a complex mixture. Bis(diisopropylamino)(2-cyanoethoxy)phosphine when used as a phosphitylating agent gave a similar result.

To investigate this result, we checked the stability of compound **5** with various tervalent phosphorus reagents using ^1H and ^{31}P NMR. It was found that compound **5** was rapidly deoxygenated within 10 min by chloro(2-cyanoethoxy)(diisopropylamino)phosphine to give **9** (Scheme 3). Deoxygenation could not be suppressed when bis(diisopropylamino)(2-cyanoethoxy)phosphine was employed. A slower but similar deoxygenation was observed when diethyl chlorophosphite was used as the phosphorus reagent.

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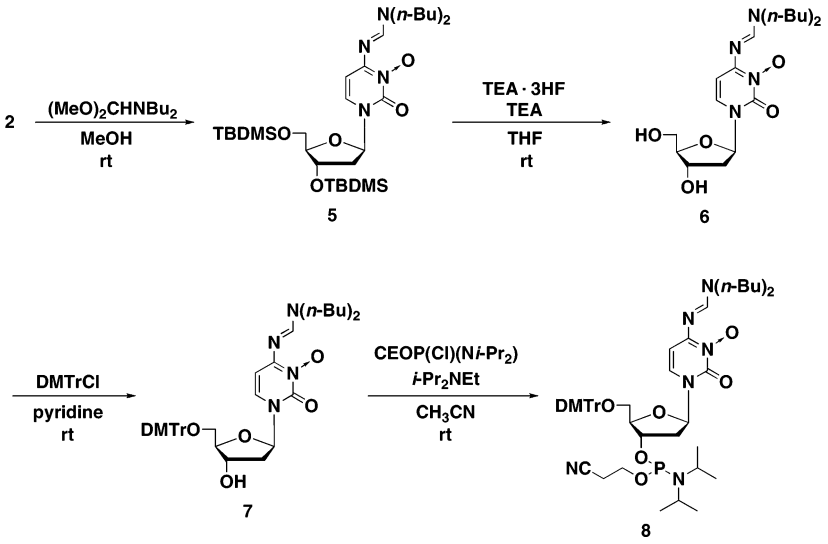
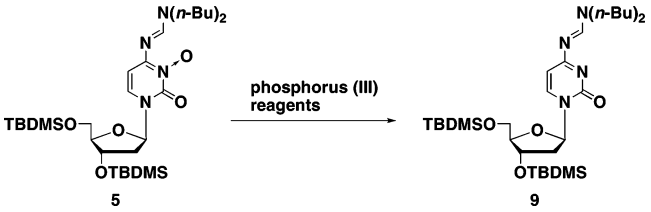
SCHEME 2. Synthesis of the 2′-Deoxycytidine N^3-Oxide 3′-Phosphoramidite Building Block 8



SCHEME 3. Deoxygenation of 5 with Phosphorus(III) Compounds



The *N*-oxide function was found to be very stable toward triethyl phosphite for at least 24 h. Interestingly, the reaction of **5** with diphenyl phosphite led to the deoxygenation of the *N*-oxide moiety ($t_{1/2}$ = 4 h). In connection with our study, Hammer has recently reported the facile reduction of a 2′-deoxynucleoside analog using a thiazole *N*-oxide nucleobase with phosphitylating reagents.[28]

Based on these results, it was concluded that the synthesis of the phosphoramide building block **8** was difficult, and it seemed that an alternative *H*-phosphonate method could not be used as suggested by its mechanism that involves activated tervalent phosphorus intermediates. Therefore, we considered that the desired oligomer should be synthesized by the selective oxidation of oligodeoxynucleotide containing *N*-free 2′-deoxycytidine or 2′-deoxyadenosine.

The synthesis of DNA dimer d[C^OT] containing dC^O was carried out, as shown in Scheme 4. A dimer with the sequence of CT was constructed on a T-loaded highly cross-linked polystyrene (HCP) according to the *N*-unprotected phosphoramidite method.[29] After removal of the 5′-terminal DMTr group, the HCP resin was treated with *m*-CPBA in MeOH. When a 0.04 M solution of *m*-CPBA in MeOH was used as the oxidizing agent at room temperature for 8 h, the cytosine residue was found to be almost quantitatively oxidized in the solid-phase (Figure 2a); however, dT was observed along with the desired dimer d[C^OpT]. It was likely that the phosphotriester bond of the d[CpT] dimer was cleaved under acidic conditions for long time periods. Therefore, the reaction time was shortened to 1 h for suppressing the generation of dT; however, the *N*-oxidation was not completed under these conditions. To improve the yield of the d[C^OpT] dimer, the concentration of mCPBA in MeOH was changed from 0.04 to 0.1 M. Under these conditions, the d[C^OpT] dimer was successfully obtained without an increase of dT (Figure 2b). Therefore, we selected a 0.1 M solution of *m*-CPBA in MeOH for 1 h as the best conditions for oxidation of the cytosine base.

Under the above-mentioned conditions, the oxidation of d[T_6-CT_7] proceeded similarly to give the desired oligomer d[$T_6C^OT_7$] in 36% yield (Figure 3a). It should be noted that the cleavage of the oligodeoxynucleotide 14mer did not occur. Similarly, a DNA 14mer d[$T_6A^OT_7$] containing 2′-deoxyadenosine *N*-oxide was synthesized by a similar postsynthetic oxidation in 27% yield (Figure 3b). These oligomers were characterized by MALDI-TOF mass spectroscopy and enzymatic hydrolysis (see the Supporting Information).

There is a possibility that 2′-deoxycytidine *N*-oxide was converted to N^4-hydroxy-2′-deoxycytidine in the DNA oligomer. To check this possibility, N^4-hydroxy-2′-deoxycytidine was synthesized by the previous method.[30] A new peak obtained by the enzymatic digestion of the modified oligomer d[$T_6C^OT_7$] was not consistent with that of 4-*N*-hydroxy-2′-deoxycytidine, as evidenced by reversed-phase HPLC analysis (Figure 4). Therefore, it seemed that 2′-deoxycytidine *N*-oxide remained intact in the DNA oligomer.

Screening of Suitable Protecting Groups Resistant to *N*-Oxidation of Nucleobases. To study the biological property of DNA incorporating a 2′-deoxynucleoside *N*-oxide, we needed DNA oligomers with appropriate sequences containing dA, dG, dC, and dT along with a damaged 2′-deoxynucleoside dC^O or dA^O. It is necessary to selectively oxidize a cytosine or adenine base at an appropriate position in the sequence and avoid side reactions on other bases by protecting them with suitable protecting groups. Acyl-type protecting groups were chosen as the protecting groups for the amino groups of dA, dG, and dC because they significantly decrease the nucleophilicity of the amino groups of the adenine and cytosine bases to prevent *N*-oxide formation. In the case of the adenine base, the acetyl

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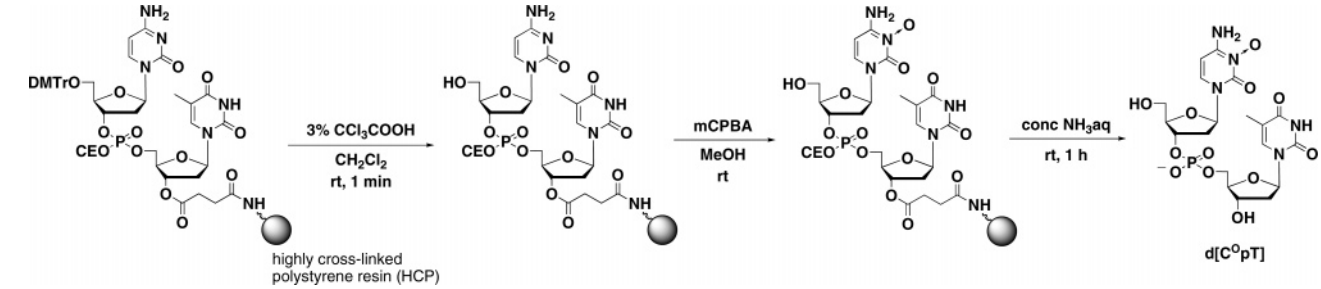
SCHEME 4. Solid-phase Synthesis of a Dimer Containing 2′-Deoxycytidine N^3-Oxide



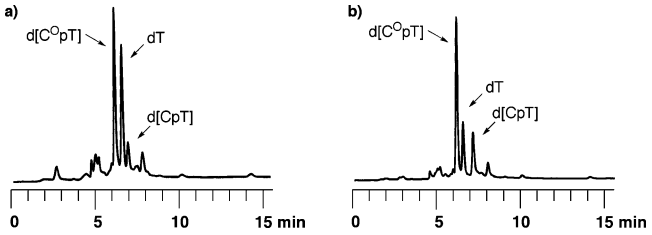


FIGURE 2. Reversed-phase HPLC profiles of the crude mixtures obtained by oxidation of the dimer d[CpT]: (a) 0.04 M mCPBA/MeOH, 8 h; (b) 0.1 M mCPBA/MeOH, 1 h.

and benzoyl groups used for the usual DNA synthesis were tested, as shown in Table 2. It was found that 4-*N*-benzoyl-2′-deoxyadenosine derivative **10b** was resistant to *m*-CPBA in MeOH and was almost recovered without *N*-oxidation of the adenine base (entry 2). In contrast, the *N*-acetylated and *N*-benzoylated 2′-deoxycytidine derivatives **11a** and **11b** formed considerable *N*-oxidation products and the recovery of these compounds was not very high (entries 3 and 4). When compound **11b** was treated with *m*-CPBA in MeOH, a complex mixture was formed. The use of the acetyl group gave a better result but the recovery of **11a** was low. Interestingly, it was found that the 4-*N*-phthaloyl-2′-deoxycytidine derivative **11c** remained completely intact as judged by TLC under these conditions and was recovered in 89% yield (entry 5).

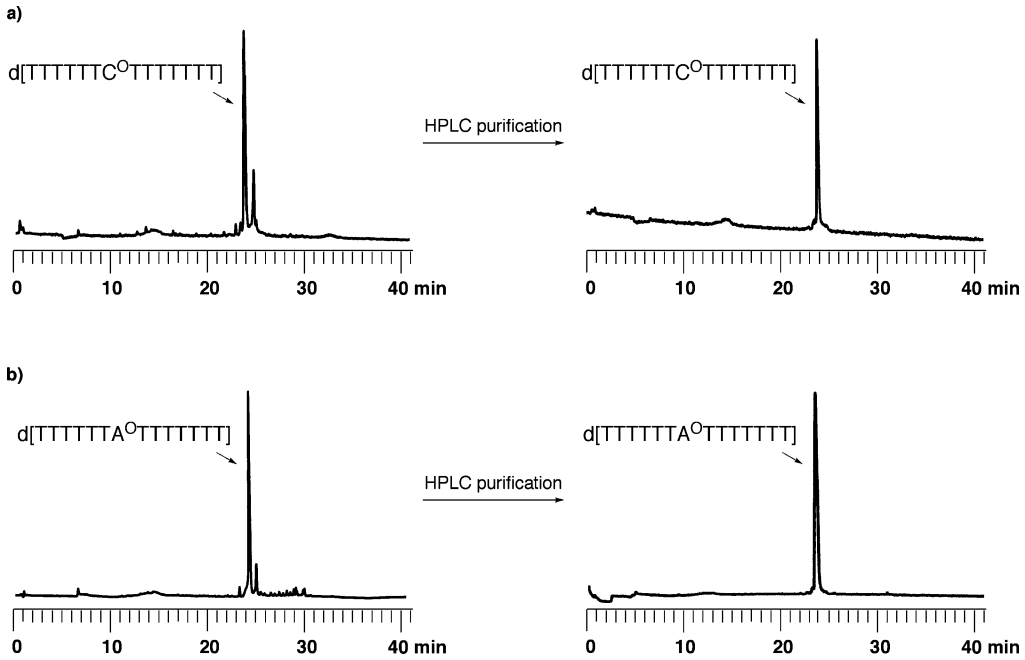


FIGURE 3. Anion-exchange HPLC profiles of the crude mixtures obtained by using a postsynthetic oxidative method (left) and the oligodeoxynucleotide obtained by HPLC purification (right): (a) d[$T_6C^OT_7$]; (b) d[$T_6A^OT_7$].

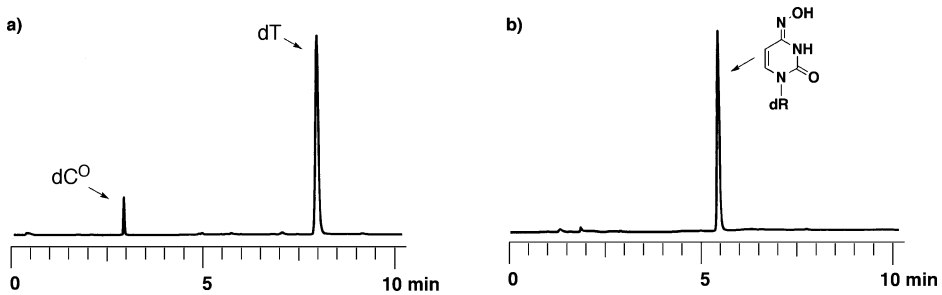
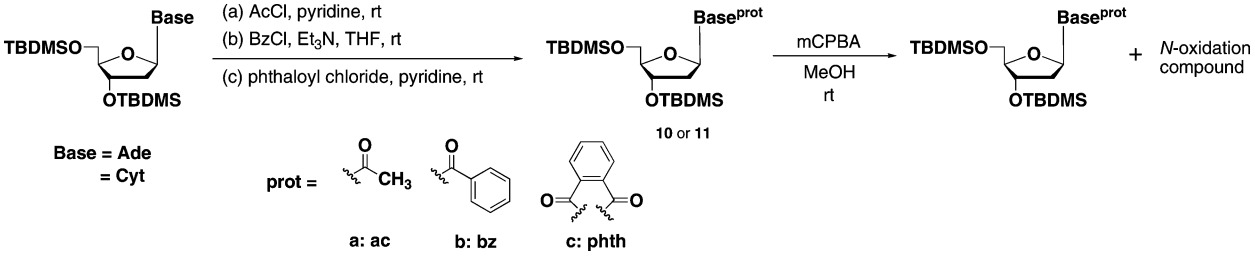


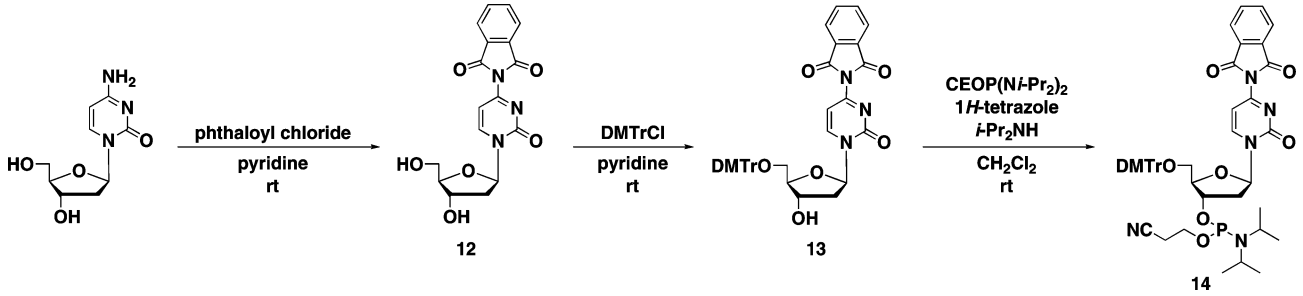
FIGURE 4. Reversed-phase HPLC profiles of (a) the 2′-deoxynucleoside obtained by enzymatic hydrolysis and (b) 4-*N*-hydroxy-2′-deoxycytidine.

TABLE 2. Stability of the Protecting Groups of the Amino Groups for the Adenine and Cytosine Bases under the Conditions for *N*-Oxidation

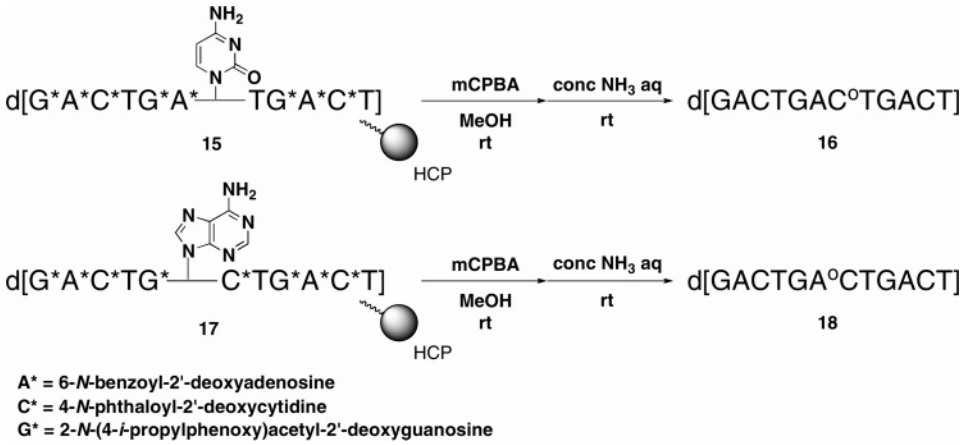


entry	compd	base	prot	recovery (%)
1	**10a**	Ade	ac	77
2	**10b**	Ade	bz	91
3	**11a**	Cyt	ac	74
4	**11b**	Cyt	bz	63
5	**11c**	Cyt	phth	89

SCHEME 5. Synthesis of a 2′-Deoxycytidine 3′-Phosphoramidite Building Block 14 Protected with a Phthaloyl Group



SCHEME 6. Solid-Phase Synthesis of DNA Oligomers 16 and 18 Containing dC^O and dA^O



Synthesis of Appropriately Protected 2′-Deoxynucleoside 3′-Phosphoramidite Building Blocks. We synthesized the 2′-deoxycytosine 3′-phosphoramidite building block **14** protected with a phthaloyl group to synthesize the desired DNA oligomers according to a previously reported method (Scheme 5).[31−33] Reaction of 2′-deoxycytidine with phthaloyl chloride in pyridine gave the 4-*N*-protected product **12** in 60% yield. The usual tritylation of **12** with DMTrCl gave the 5′-protected product **13** in 70% yield. Phosphitylation of **13** with bis(diisopropylamino)-(2-cyanoethoxy)phosphine gave the phosphoramidite unit **14**, which was isolated in 70% yield by silica gel column chromatography with 1% pyridine.

Synthesis of Oligodeoxynucleotides Incorporating dA, dG, dC, and dT Along with dC^O or dA^O. For the synthesis of DNA oligomers with appropriate sequences containing dA, dG, dC, and dT along with a damaged 2′-deoxynucleoside dC^O or dA^O, we synthesized appropriately protected DNA oligomers **15** and **17** having *N*-unprotected dA and dC, respectively, at one point in their base sequences on HCP resins. These DNA oligomers were oxidized by mCPBA in MeOH as described for *N*-oxidation. As expected, *N*-oxidation of the other bases was efficiently suppressed, and the desired DNA oligomers **16** and **18** were obtained in 13% and 11% yields, respectively, by HPLC purification (Scheme 6 and Figure 5). These oligomers were characterized by MALDI-TOF mass spectroscopy and enzymatic hydrolysis (see the Supporting Information).

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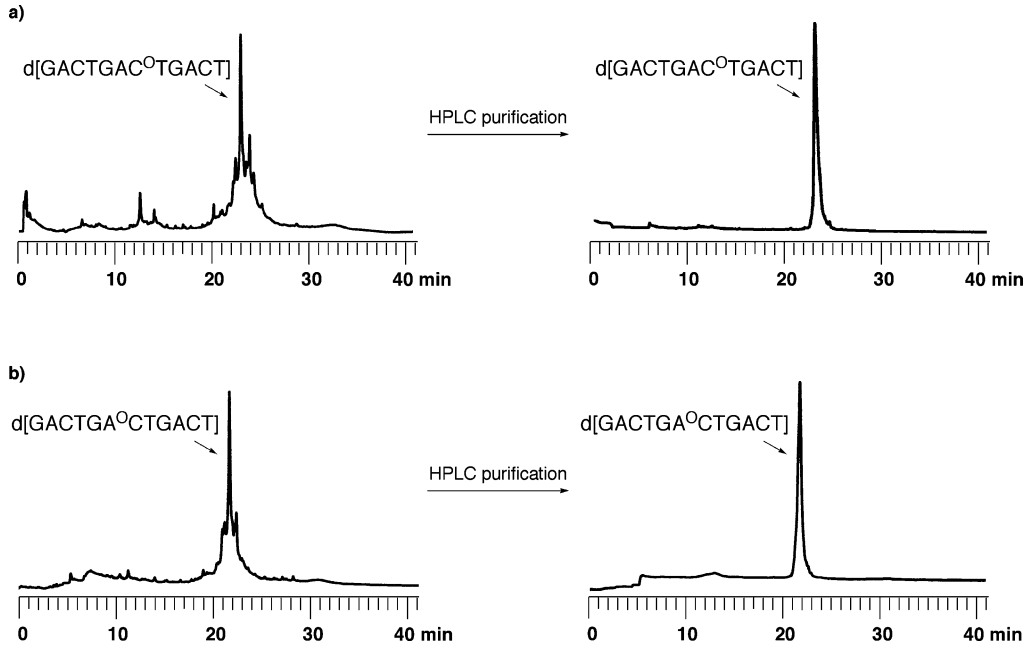

FIGURE 5. Anion-exchange HPLC profiles of the crude mixtures obtained by using a postsynthetic oxidative method (left) and the desired oligodeoxynucleotide obtained by HPLC purification (right): (a) oligodeoxynucleotide **16**; (b) oligodeoxynucleotide **18**.

Conclusion

In this study, we have synthesized oligodeoxynucleotides containing 2′-deoxycytidine or 2′-deoxyadenosine *N*-oxide. It was difficult to prepare the 2′-deoxynucleoside *N*-oxide 3′-phosphoramidite derivatives required for the usual protocol in the phosphoramidite approach. This is because the *N*-oxide function was very sensitive to tervalent phosphorus species. To overcome this inherent problem, we tried to use the postsynthetic approach using our recently reported *N*-unprotected phosphoramidite method.[29] Thus, we synthesized the desired oligodeoxynucleotides with modified bases. Using established methods, we were unable to synthesize oligomers having nucleoside *N*-oxide, while the synthesis based on the postsynthetic modification method was successful without deoxygenation of *N*-oxide. In addition, we were able to synthesize oxidized oligomers having various sequences using appropriate base-protecting groups. Further biological studies on the properties of modified oligodeoxynucleotides with dC^O or dA^O are now under way.

Experimental Section

Oxidation of 1 to 2 by Use of Various Oxidizing Agents. The conditions used for these experiments are shown in Table 1. Typical procedure: Compound **1** (45.6 mg, 0.10 mmol) was dissolved in a solvent (1 mL), and the solution was treated with an oxidizing agent for an appropriate time. The reaction was monitored by TLC analysis. The reaction mixture was diluted with $CHCl_3$ (10 mL) and washed with aqueous $NaHCO_3$. The organic phase was collected, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with $CHCl_3$−MeOH (100:0−95:5, v/v) to give the fractions containing **2**. The fractions were collected and evaporated under reduced pressure to give **2**. The yields of **2** are listed in Table 1: UV (MeOH) λ_{max} 274 nm, λ_{max} 227 nm; ^{1}H NMR ($CDCl_3$) δ 0.00−0.05 (m, 12H), 0.82−0.86 (m, 18H), 2.00−2.09 (m, 1H), 2.30−2.39 (m, 1H), 3.71 (dd, 1H, J = 2.9 Hz, J = 12.0 Hz), 3.83−3.85 (m, 2H), 4.31−4.37 (m, 1H), 6.22 (t, 1H, J = 5.4 Hz), 6.46 (d, 1H, J = 7.4 Hz), 7.73 (d, 1H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ −5.6, −5.5, −4.9, −4.6, 17.9, 18.3, 25.7, 25.9, 42.0, 61.9, 70.3, 86.6, 87.7, 131.8, 149.2, 155.4; HRMS (ESI) *m*/*z* (M + H) calcd for $C_{21}H_{42}N_3O_5Si_2^+$ 472.2678, found 472.2650.

Oxidation of 3 to 4 by Use of *m*-CPBA. The conditions used for these experiments are shown in Table 2. Typical procedure: Compound **3** (192.0 mg, 0.40 mmol) was dissolved in MeOH (4 mL), and this solution was treated with *m*-CPBA for an appropriate time. The reaction was monitored by TLC analysis. The reaction mixture was diluted with $CHCl_3$ (40 mL) and washed with aqueous $NaHCO_3$. The organic phase was collected, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with $CHCl_3$−MeOH (100:0−95:5, v/v) to give the fractions containing **4**. The fractions were collected and evaporated under reduced pressure to give **4**. The yields of **4** are listed in Table 2. Compound **4**: UV (MeOH) λ_{max} 262 nm, λ_{max} 234 nm; ^{1}H NMR ($CDCl_3$) δ 0.09−0.11 (m, 12H), 0.91−0.92 (m, 18H), 2.41−2.50 (m, 1H), 2.57−2.67 (m, 1H), 3.77 (dd, 1H, J = 3.1 Hz, J = 11.2 Hz), 3.88 (dd, 1H, J = 4.0 Hz, J = 11.2 Hz), 4.01−4.05 (m, 1H), 4.58−4.63 (m, 1H), 6.40 (t, 1H, J = 6.3 Hz), 7.35 (br s, 2H), 8.25 (s, 1H), 8.70 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.4, −4.8, −4.7, 17.9, 18.26, 25.7, 25.92, 41.3, 62.6, 71.7, 84.6, 88.0, 119.4, 141.5, 142.1, 143.9, 148.6; HRMS (ESI) *m*/*z* (M + H) calcd for $C_{22}H_{42}N_5O_4Si_2^+$ 496.2770, found 496.2774.

Synthesis of Compound 5. Compound **2** (472 mg, 1.0 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine (1 mL × 3), dry toluene (1 mL × 1), and dry CH_3CN (1 mL ×1) and dissolved in dry MeOH (10 mL). To the solution was added *N*,*N*-dibutylformamide dimethyl acetal (610 mg, 3.0 mmol). After being stirred at room temperature for 1 h, the solution was evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with hexane−$CHCl_3$ (25:75−0:100, v/v) and then $CHCl_3$−MeOH (100:0−95:5, v/v) to give the fractions containing **5**. The fractions were collected and evaporated under reduced pressure to give **5** (603 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 0.00−0.06 (m, 12H), 0.84−0.91 (m, 24H) 1.26−1.37 (m, 2H), 1.51−1.62 (m, 2H), 2.05−2.14 (m, 1H), 2.37−2.46 (m, 1H), 3.39 (br s, 2H), 3.72 (d, 1H, J = 9.6 Hz), 3.87−3.91 (m, 2H), 4.30−4.36 (m, 1H), 5.92 (d, 1H, J = 7.6 Hz), 6.24 (t, 1H, J = 5.4 Hz), 7.69 (d, 1H, J = 7.6 Hz), 10.58 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.6, −5.5, −5.0, −4.6, 13.6, 13.7, 17.9, 18.3, 19.6, 20.1, 25.7, 25.9,

29.3, 30.7, 41.8, 42.0, 47.1, 61.7, 69.8, 87.1, 87.7, 102.7, 128.5, 151.5, 154.4, 159.6; HRMS (ESI) *m/z* (M + H) calcd for $C_{30}H_{59}N_4O_5Si_2^+$ 611.4019, found 611.4010.

Synthesis of Compound 7. To a solution of compound **5** (1.22 g, 2.0 mmol) in dry THF (10 mL) were added triethylamine trihydrofluoride (977 μL, 6.0 mmol) and triethylamine (836 μL). After being stirred at room temperature for 2 h, the reaction was quenched by addition of H_2O. The mixture was partitioned between $CHCl_3$/*i*-PrOH (3:1, v/v) and H_2O. The organic phase was collected, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Subsequently, the residue was rendered anhydrous by repeated coevaporation with dry pyridine (1 mL × 1) and dissolved in dry pyridine (20 mL). To the solution was added DMTrCl (813 mg, 2.4 mmol), and the mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$. The mixture was partitioned between $CHCl_3$ and H_2O. The organic phase was collected, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with $CHCl_3$−MeOH (100:0−95:5, v/v) containing 0.5% Et_3N to give the fractions containing **7**. The fractions were collected and evaporated under reduced pressure. The residue was evaporated by repeated coevaporation three times each with toluene and $CHCl_3$ to remove the last traces of Et_3N to give **7** (979 mg, 71%): ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 6H, J = 7.2 Hz), 1.26−1.36 (m, 2H), 1.54−1.65 (m, 2H), 2.21−2.30 (m, 1H), 2.62−2.71 (m, 1H), 3.36−3.50 (m, 4H), 3.73−3.78 (m, 8H), 4.18−4.20 (m, 1H), 4.49−4.55 (m, 1H), 5.75 (d, 1H, J = 7.7 Hz), 6.33 (t, 1H, J = 5.5 Hz), 6.83 (d, 4H, J = 8.7 Hz), 7.26−7.42 (m, 9H), 7.66 (d, 1H, J = 7.7 Hz), 10.43 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.8, 29.1, 30.6, 41.9, 44.5, 52.1, 55.1, 62.9, 70.4, 86.4, 86.5, 87.8, 102.5, 113.1, 126.8, 127.8, 128.1, 129.4, 130.0, 130.1, 130.3, 130.5, 144.5, 151.4, 154.7, 158.4, 159.5; HRMS (ESI) *m/z* (M + H) calcd for $C_{39}H_{49}N_4O_7^+$ 685.3596, found 685.3593.

Deoxygenation of 5 by Use of Various Phosphorus Reagents. The conditions used for these experiments are shown in Scheme 3. Typical procedure: Compound **5** (61.1 mg, 0.10 mmol) was dissolved in CH_3CN (1 mL), and this solution was treated with a phosphorus agent for an appropriate time. The reaction was monitored by TLC analysis. The reaction mixture was diluted with $CHCl_3$ (10 mL) and washed once with aqueous $NaHCO_3$. The organic phase was collected, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with $CHCl_3$−MeOH (100:0−95:5, v/v) to give the fractions containing **9**. The fractions were collected and evaporated under reduced pressure to give **9**: ^{1}H NMR ($CDCl_3$) δ 0.00−0.07 (m, 12H), 0.83−0.91 (m, 24H), 1.26−1.34 (m, 2H), 1.49−1.60 (m, 2H), 2.06−2.12 (m, 1H), 2.36−2.46 (m, 1H), 3.21−3.32 (m, 2H), 3.43−3.54 (m, 2H), 3.73 (dd, 1H, J = 2.3 Hz, J = 11.5 Hz), 3.82−3.93 (m, 2H), 4.31−4.38 (m, 1H), 5.95 (d, 1H, J = 7.3 Hz), 6.27 (t, 1H, J = 5.5 Hz), 8.06 (d, 1H, J = 7.3 Hz), 8.78 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.59, −5.55, −5.0, −4.6, 13.6, 13,7, 17.9, 18.3, 19.7, 20.0, 25.7, 25.9, 29.0, 30.9, 42.2, 45.2, 52.0, 61.7, 69.7, 86.0, 87.1, 102.4, 141.3, 156.3, 158.1, 171.8; HRMS (ESI) *m/z* (M + H) calcd for $C_{30}H_{59}N_4O_4Si_2^+$ 595.4069, found 595.4069.

Synthesis of Compound 11c. Compound **2** (228 mg, 0.50 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine (1 mL × 1) and dissolved in dry pyridine (5 mL). To the solution was added phthaloyl chloride (86.4 mg, 0.6 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with $CHCl_3$ (10 mL) and washed with aqueous $NaHCO_3$. The organic phase was collected, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with $CHCl_3$−MeOH (100:0−98:2, v/v) to give the fractions containing **11c**. The fractions were collected and evaporated under reduced pressure to give **11c** (246 mg, 84%): ^{1}H NMR ($CDCl_3$) δ 0.05−0.11 (m, 12H), 0.86−0.91 (m, 18H), 2.20−2.23 (m, 1H), 2.53−2.63 (m, 1H), 3.76−4.01 (m, 2H), 4.34−4.42 (m, 1H), 6.19−6.23 (m, 1H), 6.61 (d, 1H, J = 7.3 Hz), 7.79−7.83 (m, 2H), 7.95−7.98 (m, 2H), 8.63 (d, 1H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.4, −4.9, −4.5, 18.0, 18.4, 25.7, 25.7, 25.90, 25.94, 42.1, 61.5, 69.4, 87.5, 87.9, 100.4, 124.4, 131.5, 135.1, 145.4, 154.7, 159.1, 165.1; HRMS (ESI) *m/z* (M + H) calcd for $C_{29}H_{44}N_3O_6Si_2^+$ 586.2763, found 586.2762.

Stability of 10a,b and 11a−c under Conditions for *N*-Oxidation. The conditions used for these experiments are shown in Table 2. Typical procedure: The compound (0.10 mmol) was dissolved in MeOH (1 mL), and *m*-CPBA (22.4 mg, 0.10 mmol; 77% purity) was added. After being stirred at room temperature for 24 h, the reaction mixture was diluted with $CHCl_3$ (10 mL) and washed with aqueous $NaHCO_3$. The organic phase was collected, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with $CHCl_3$−MeOH (100:0−95:5, v/v) to give the fractions containing starting material. The fractions were collected and evaporated under reduced pressure to give starting material. The recovery yields of **10a**,**b** and **11a−c** are listed in Table 2.

Synthesis of Compound 12. 2′-Deoxycytidine monohydride (2.27 g, 10.0 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine (2 mL × 1) and dissolved in dry pyridine (36 mL). To the solution was added chlorotrimethylsilane (3.16 mL, 25.0 mmol), and the mixture was stirred for 1 h. Then DMAP (10 mg) was added, and phthaloyl chloride (2.16 mL, 15.0 mmol) in dioxane (4 mL) was added dropwise at 0 °C for 15 min. After being stirred at room temperature for 1 h, the mixture was hydrolyzed with ice−water, and stirring was continued for 15 min. The mixture was partitioned between 10% pyridine in $CHCl_3$ and H_2O. The organic phase was extracted with H_2O (50 mL), and the combined aqueous phases were washed twice with 10% pyridine in $CHCl_3$ (50 mL). The organic phase was collected, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was evaporated by repeated coevaporation with toluene and CH_3CN to remove pyridine. The residue was washed with CH_2Cl_2 to give **12** (2.13 g, 60%): ^{1}H NMR (DMSO) δ 2.10−2.16 (m, 1H), 2.36−2.43 (m, 1H), 3.57−3.68 (m, 2H), 3.90−3.94 (m, 1H), 4.21−4.28 (m, 1H), 5.11 (t, 1H, J = 5.2 Hz), 5.30 (d, 1H, J = 4.3 Hz), 6.11 (t, 1H, J = 6.2 Hz), 6.71 (d, 1H, J = 7.1 Hz), 7.92−8.03 (m, 4H), 8.63 (d, 1H, J = 7.3 Hz); ^{13}C NMR (DMSO) δ 40.9, 60.7, 69.7, 87.1, 88.3, 101.1, 124.0, 131.2, 135.4, 146.0, 154.2, 158.9, 165.1; HRMS (ESI) *m/z* (M + H) calcd for $C_{17}H_{16}N_3O_6^+$ 358.1034, found 358.1038.

Synthesis of Compound 13. Compound **12** (715 mg, 2.0 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine (1 mL × 1) and dissolved in dry pyridine (20 mL). To the solution was added DMTrCl (813 mg, 2.4 mmol), and the mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$. The mixture was partitioned between $CHCl_3$ and H_2O. The organic phase was collected, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with hexane−ethyl acetate (25:75, v/v) containing 1% pyridine to give the fractions containing **13**. The fractions were collected and evaporated under reduced pressure. The residue was finally evaporated by repeated coevaporation three times each with toluene and $CHCl_3$ to remove the last traces of pyridine to give **13** (920 mg, 70%): ^{1}H NMR ($CDCl_3$) δ 2.36−2.40 (m, 1H), 2.67−2.77 (m, 1H), 3.42 (dd, 1H, J = 3.4 Hz, J = 11.3 Hz), 3.52 (dd, 1H, J = 2.7 Hz, J = 11.1 Hz), 3.75 (s, 6H), 4.12−4.13 (m, 1H), 4.54−4.60 (m, 1H), 6.21 (t, 1H, J = 5.4 Hz), 6.37 (d, 1H, J = 7.1 Hz), 6.81 (d, 4H, J = 8.7 Hz), 7.11−7.37 (m, 9H), 7.75−7.79 (m, 2H), 7.90−7.93 (m, 2H), 8.54 (d, 1H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 41.7, 55.1, 62.1, 69.6, 86.3, 86.6, 87.7, 100.5, 113.2, 124.2, 126.9, 127.9, 128.1, 129.9, 131.1, 135.0, 135.3, 135.4, 144.1, 145.5, 155.0, 158.4, 159.0, 164.8; HRMS (ESI) *m/z* (M + H) calcd for $C_{38}H_{34}N_3O_8^+$ 660.2340, found 660.2349.

Synthesis of Compound 14. Compound **13** (990 mg, 1.5 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine (1 mL × 3), dry toluene (1 mL × 1), and dry CH_3CN (1

mL × 1) and dissolved in dry CH_2Cl_2 (15 mL). To the solution were added bis(diisopropylamino)(2-cyanoethoxy)phosphine (524 μL, 1.65 mmol), 1*H*-tetrazole (63.2 mg, 0.90 mmol), and diisopropylamine (127 μL, 0.90 mmol), and the mixture was stirred at room temperature for 2 h. The mixture was partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic phase was collected, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with hexane−ethyl acetate (40:60−30:70, v/v) containing 1% pyridine to give the fractions containing **13**. The fractions were collected and evaporated under reduced pressure. The residue was finally evaporated by repeated coevaporation three times each with toluene and $CHCl_3$ to remove the last traces of pyridine to give **13** (900 mg, 70%): ^{1}H NMR ($CDCl_3$) δ 1.04−1.17 (m, 12H), 2.40−2.45 (m, 2H), 2.62 (t, 1H, J = 6.3 Hz), 2.72−2.82 (m, 1H), 3.40−3.61 (m, 6H), 3.78 (s, 6H), 4.20−4.21 (m, 1H), 4.59−4.69 (m, 1H), 6.22−6.32 (m, 2H), 6.81−6.86 (m, 4H), 7.26−7.39 (m, 9H), 7.79−7.82 (m, 2H), 7.94−7.97 (m, 2H), 8.51 and 8.60 (2d, 1H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 20.1, 20.2, 20.4, 24.4, 24.5, 24.6, 40.7, 41.1, 43.1, 43.2, 43.3, 53.4, 55.2, 58.1, 58.4, 61.5, 61.9, 70.9, 71.2, 71.8, 72.1, 85.8, 86.9, 87.5, 87.6, 100.5, 113.2, 117.3, 117.5, 124.3, 127.1, 128.0, 128.1, 128.2, 130.07, 130.13, 131.4, 135.1, 135.3, 144.0, 145.2, 154.6, 158.6, 159.1, 164.9; ^{31}P NMR ($CDCl_3$) δ 149.6, 150.2 (2s); HRMS (ESI) *m*/*z* (M + H) calcd for $C_{47}H_{51}N_5O_9P^+$ 860.3419, found 860.3411.

Synthesis of the Dimer d[C^{O}pT]. A thymidine-loaded HCP (1.0 μmol, 27 μmol/g, succinate linker) was used. Each cycle of chain elongation consisted of the following steps: (1) detritylation (3% trichloroacetic acid in CH_2Cl_2, 2 mL, 1 min); (2) washing [CH_2Cl_2 (1 mL × 3), CH_3CN (1 mL × 3)]; (3) the first coupling [an appropriate phosphoramidite unit (20 μmol) in CH_3CN (200 μL), HOBt (5.4 mg, 40 μmol) in CH_3CN (200 μL), 1 min]; (4) washing [CH_3CN (1 mL × 3)]; (5) the second coupling [an appropriate phosphoramidite unit (20 μmol) in CH_3CN (200 μL), HOBt (5.4 mg, 40 μmol) in CH_3CN (200 μL), 1 min]; (6) washing [CH_3CN (1 mL × 3)]; (7) oxidation [0.1 M I_2, pyridine−H_2O (9/1, v/v), 2 min]; and (8) washing [pyridine (1 mL × 3), CH_3CN (1 mL × 3), CH_2Cl_2 (1 mL × 3)]. Generally, the average yield per cycle was estimated to be 98−99% by the DMTr cation assay. After chain elongation was finished, the DMTr group was removed by treatment with 3% trichloroacetic acid in CH_2Cl_2 (2 mL) for 1 min, and the resin was washed with CH_2Cl_2 (1 mL × 3), CH_3CN containing 1% Et_3N (1 mL × 3), and CH_3CN (1 mL × 3). Subsequently, the synthesized dimer d[CpT]-loaded HCP (50 nmol, 27 μmol/g, succinate linker) was used. General procedure for *N*-oxidation reaction: (1) Oxidation [0.02−0.1 M *m*-CPBA in MeOH, 1−8 h]; (2) washing [MeOH (1 mL × 3), CH_3CN (1 mL × 3)]. The dimer was deprotected and released from the polymer support by treatment with concentrated NH_3 aq (500 μL) for 1 h. The polymer support was removed by filtration and washed with CH_3CN (1 mL × 3). The filtrate was evaporated and purified by reversed-phase HPLC: HRMS (ESI) *m*/*z* (M + H) calcd for $C_{19}H_{27}N_5O_{12}P^+$ 548.1388, found 548.1388.

Synthesis of Oligodeoxynucleotides d[$T_6C^OT_7$] and d[$T_6A^OT_7$]. The synthesis of oligodeoxyribonucleotides by use of an ABI 392 DNA synthesizer was carried out.[21] After chain elongation was finished, the DMTr group was removed by treatment with 3% trichloroacetic acid in CH_2Cl_2 (2 mL) for 1 min, and the resin was washed with CH_2Cl_2 (1 mL × 3), CH_3CN containing 1% Et_3N (1 mL × 3), and CH_3CN (1 mL × 3). In the synthesis of a DNA 14mer containing a 2′-deoxynucleoside *N*-oxide, the unmodified oligomer-loading HCP (250 nmol, 27 μmol/g, succinate linker) was oxidized by treatment of a solution of 0.1 M *m*-CPBA in MeOH (150 μL) and washed with MeOH (1 mL × 3) and CH_3CN (1 mL × 3). The oligomer was deprotected and released from the polymer support by treatment with concentrated NH_3 aq (500 μL) for 1 h. The polymer support was removed by filtration and washed with distilled water (1 mL × 3). The filtrate was evaporated and purified by reversed-phase HPLC or anion-exchange HPLC.

The mass spectral data of oligodeoxynucleotides are as follows. Oligodeoxynucleotide d[$T_6C^OT_7$]: MALDI-TOF mass (M + H) calcd for $C_{140}H_{185}N_{29}O_{95}P_{13}^+$ 4194.71, found 4198.69. Oligodeoxynucleotide d[$T_6A^OT_7$]: MALDI-TOF mass (M + H) calcd for $C_{141}H_{185}N_{31}O_{94}P_{13}^+$ 4218.72, found 4222.71.

Synthesis of Oligodeoxynucleotides 16 and 18. The synthesis of oligodeoxyribonucleotides by use of an ABI 392 DNA synthesizer was carried out.[21] After chain elongation was finished, the DMTr group was removed by treatment with 3% trichloroacetic acid in CH_2Cl_2 (2 mL) for 1 min, and the resin was washed with CH_2Cl_2 (1 mL × 3), CH_3CN containing 1% pyridine (1 mL × 3), and CH_3CN (1 mL × 3). In the synthesis of a DNA 14mer containing a 2′-deoxynucleoside *N*-oxide, the unmodified oligomer-loading HCP (250 nmol, 27 μmol/g, succinate linker) was oxidized by treatment of a solution of 0.1 M *m*-CPBA in MeOH (150 μL), and washed with MeOH (1 mL × 3) and CH_3CN (1 mL × 3). The oligomer was deprotected and released from the polymer support by treatment with concentrated NH_3 aq (500 μL) for 12 h. The polymer support was removed by filtration and washed with distilled water (1 mL × 3). The filtrate was evaporated and purified by reversed-phase HPLC or anion-exchange HPLC. The yields of these modified oligodeoxynucleotides were calculated using the ε value of this oligonucleotide, which was estimated by the sum of the ε values at 260 nm of all nucleotides involving the modified nucleoside in consideration of a 15% hyperchromic effect: dA^O, ε = 7.93 × 10^3 at 260 nm; dC^O, ε = 3.91 × 10^3 at 260 nm. For the modified oligodeoxynucleotides, the following ε was used: d[$T_6C^OT_7$], ε = 9.95 × 10^4 at 260 nm; d[$T_6A^OT_7$], ε = 1.03 × 10^5 at 260 nm; d[GACTGAC^{O}TGACT] **16**, ε = 1.09 × 10^5 at 260 nm; d[GACTGA^{O}CTGACT] **18**, ε = 1.05 × 10^5 at 260 nm.

The mass spectral data of oligodeoxynucleotides are as follows. Oligodeoxynucleotide **16**: MALDI-TOF Mass (M + H) calcd for $C_{117}H_{149}N_{45}O_{71}P_{11}^+$ 3660.65, found 3660,08. Oligodeoxynucleotide **18**: MALDI-TOF mass (M + H) calcd for $C_{117}H_{149}N_{45}O_{71}P_{11}^+$ 3660.65, found 3664.44.

Enzyme Assay of Oligodeoxynucleotides. The enzymatic digestion was performed by using an appropriate oligodeoxynucleotide (0.2 OD), snake venom phosphodiesterase (10 μg), nuclease P1 (10 μg), and calf intestine alkaline phosphatase (0.4 units) in 20 μL of alkaline phosphatase buffer [500 mM Tris-HCl (pH 9.0), 10 mM $MgCl_2$] at 37 °C for 4 h. After the enzymes were deactivated by heating at 80 °C for 5 min, the solution was diluted and filtered by a 0.45 μm filter (Millex-HV, Millipore). The mixture was analyzed by reversed-phase HPLC. For d[$T_6C^OT_7$], dC^O:dT = 1.0:13.1. For d[$T_6A^OT_7$], dA^O:dT = 1.0:13.0. For oligodeoxynucleotide **16**, dC^O:dG:dA:dC:dT = 1.0:3.2:2.9:2.0:3.0. For oligodeoxynucleotide **18**, dA^O:dG:dA:dC:dT = 1.0:3.2:2.0:3.0:3.1.

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Supporting Information Available: The ^{1}H, ^{13}C, and ^{31}P NMR data of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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