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（要　旨）
(Summary)

To the best of our knowledge, there have been almost none of the previous report about the chemical modification of oligonucleotide with anionic nucleobase containing carboxy group capable of interacting with its complementary nucleobase by hydrogen bond. Recently the research of the modified oligonucleotides endowed with external stimuli-responsive properties have become interesting. We had hypothesized that a benzoic acid residue incorporated into oligonucleotides could provide them with pH-responsive duplex forming abilities because the arrangements of hydrogen bond donor and acceptor in its both protonated and deprotonated forms seems to be complementary to those of natural nucleobases. Throughout the study, we have demonstrated the method to incorporate a benzoic acid residue or its derivative into oligonucleotides by the phosphoramidite approach with the main purpose to create the pH-responsive oligonucleotides. The effect of pH on thermal stabilities and nucleobase selectivities were analyzed based on UV thermal denaturation experimental results over a pH range from 5.0 to 8.0.

In chapter 2 we have achieved the incorporation of a benzoic acid residue on a deoxyribose backbone (X_1), a benzoic acid residue incorporated on a D-threoninol backbone (X_2), and an isophthalic acid residue incorporated on a D-threoninol backbone (X_3) into oligonucleotides. We found that the oligonucleotide containing X_3 is capable of changing its preferential base pair from X_3·dA to X_3·dG in response to a change in pH from 5.0 to 7.0 (or 8.0), without significantly changing the duplex stability. This is, to the best of our knowledge, the first example in which the non-natural nucleobase analog has been demonstrated with the capability of base pair switching in response to a pH change without a dramatic change in thermal stability of

the DNA duplex. In addition, we also found out that X_1, X_2,or X_3 exhibit selectivity most highly toward cytosine under mild acidic condition, especially at pH 5.0.

In Chapter 3 we have accomplished the incorporation of an *ortho*-Cl substituted benzoic acid residue on a deoxyribose backbone ($^{Cl}X_1$) with an aim to create the oligonucleotide exhibiting pH-dependent cytosine selectivity with increased pH sensitivity at a pH range of 6.0−7.0. We found that the incorporated $^{Cl}X_1$ residue reduced stabilities when forming duplexes more than the X_1 did. This was consistent with *ab nitio* calculation performed to estimate the C1'−C1' distance across the $^{Cl}X_1$·dC pair in comparison with the X_1·dC and dG·dC pair. According to the calculation, the C1'−C1' distance across the $^{Cl}X_1$·dC pair deviated more from the distance across the standard dG·dC pair than the distance across the X_1·dC pair did. However, as expected, the incorporated $^{Cl}X_1$ residue increased the degree of pH sensitivity at a pH range of 6.0−7.0 more than the X_1 residue did. Thus, in short, to advantageously choose either X_1 or $^{Cl}X_1$ in order to create a modified oligonucleotide that exhibits pH-sensitive selectivity toward cytosine, thermal stability when forming duplexes should also be taken into account.

In Chapter 4 we have successfully designed and synthesized gapmer oligonucleotides modified with two X_1 residues (**GM 1**) or three X_1 residues (**GM 2**) with a final goal to create a smart antisense oligonucleotide displaying intrinsic pH-responsive cytosine selectivity. We found that the thermal stabilities of the duplex formed between **GM 1** and its complementary RNA are higher than those of the duplex formed between **GM 1** and its complementary DNA, being consistent with general scientific acceptance. However, the pH sensitivity of **GM 1** at a pH range of 6.0−7.0 reduced when it forms a duplex with complementary RNA by approximately a factor of 2. Next, when the number of X_1 modification was increased to three (**GM 2**), the pH sensitivity at a pH range of 6.0−7.0 significantly increased by approximately a factor of 2, but the thermal stabilities

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