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Novel specific binding of copper ions to naturally modified base pairs involving 5-fluorouracil in duplex DNA†

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Only mercury(II) and silver(I) ions are known to specifically bind to natural and naturally modified base pairs in duplex DNA to form metal-mediated base pairs. We found novel, specific binding of copper ions to naturally modified base pairs involving 5-fluorouracil (FdU) in duplex DNA, forming C–Cu–FdU and FdU–Cu–C base pairs.

The interactions of metal ions with nucleic acids play a role in the structural formation and folding of nucleic acids by reducing electrostatic repulsion among nucleic acid phosphate backbones,[1–5] as well as in the biological functions of nucleic acids, such as the catalytic activity of ribozymes and DNAzymes.[6–10] These interactions also have potential applications in nanotechnology, including the development of biomolecular nanomaterials, nanomachines, and nanodevices.[11–14]

Several synthetic artificial mismatched base pairs in duplex DNA have been developed to interact with various metal ions, thereby forming novel metal-mediated artificial base pairs.[1,15–18] Tanaka and Shionoya first synthesized a novel artificial metal ion–nucleoside complex as an alternative to natural Watson–Crick base pairs.[15] Meggers, Romesberg, and Schultz were the first to synthesize and introduce metal ion-artificial base pair chemistry into duplex DNA.[16]

Natural mismatched base pairs in duplex DNA specifically bind to metal ions to form T–Hg–T [19–27] and C–Ag–C [23,26,28–35] metal-mediated base pairs. UV melting analyses have shown that the melting temperatures (T_m) of duplex DNAs involving T–T or C–C base pairs significantly increase upon the addition of Hg^{2+} and Ag^{+}, respectively,[19,20,22,28,30] whereas those of the corresponding duplex DNAs with perfectly matched or other mismatched base pairs do not change significantly.[22,30] Importantly, the T_m values of duplex DNAs involving T–T and C–C base pairs do not increase significantly upon the addition of other metal ions (Mg^{2+}, Ca^{2+}, Mn^{2+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Ru^{3+}, Pd^{2+}, Cd^{2+}, and Pb^{2+}).[19,20,28,30] Thus, the increased T_m of duplex DNAs involving T–T and C–C base pairs upon the addition of Hg^{2+} and Ag^{+}, respectively, is highly specific. Isothermal titration calorimetric and X-ray crystallographic analyses have revealed that Hg^{2+} and Ag^{+} bind directly to the T–T and C–C base pairs, respectively, in a 1 : 1 molar ratio to form T–Hg–T and C–Ag–C base pairs.[22,24,25,29–31,35] Thus, the direct binding of Hg^{2+} and Ag^{+} specifically increases the T_m of duplex DNAs involving T–T and C–C base pairs, respectively.

UV melting experiments indicate that naturally modified mismatched base pairs involving 5-fluorouracil (FdU) in duplex DNA, FdU–FdU, bind to Hg^{2+} and Ag^{+} at molar ratios of 1 : 1 and 1 : 2, respectively, to form FdU–Hg–FdU and FdU–2Ag–FdU base pairs.[36] UV melting experiments and X-ray crystallographic analyses revealed similar binding patterns for two other naturally modified mismatched base pairs, 2-thiothymine–2-thiothymine (S2–S2) and 4-thiothymine–4-thiothymine (S4–S4), in duplex DNA upon binding to Hg^{2+} and Ag^{+} at molar ratios of 1 : 1 and 1 : 2, respectively, to form S2–Hg–S2, S4–Hg–S4, S2–2Ag–S2, and S4–2Ag–S4 base pairs.[37,38] The thermal stability of duplex DNAs involving S2–S2 and S4–S4 base pairs did not change significantly upon the addition of other metal ions (Mg^{2+}, Ca^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Pd^{2+}, Cd^{2+}, and Pt^{2+}),[37] indicating the metal ion specificity of the S2–Hg–S2, S4–Hg–S4, S2–2Ag–S2, and S4–2Ag–S4 base pairs.

As described above, only Hg^{2+} and Ag^{+} metal ions are known to specifically bind to natural and naturally modified mismatched base pairs in duplex DNA. In the present study, we examined the possibility of specific binding by metal ions other than Hg^{2+} and Ag^{+} to naturally modified mismatched base pairs in duplex DNA. Using UV melting and X-ray crystallography, we identified specific binding of copper ions to naturally modified mismatched base pairs involving FdU, namely C–FdU and FdU–C, in duplex DNA, forming C–Cu–FdU and FdU–Cu–C base pairs, respectively. The chemical structures of

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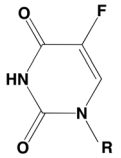
(a) 5-fluorouracil (FdU)



(b)
F25**X**: 5'-d(GCCCTGCCTGTC**X**CCCAGATCACTG)-3'
R25**Y**: 3'-d(CGGGACGGACAG**Y**GGGTCTAGTGAC)-5'
(**X–Y**:A–A, A–C, A–G, A–T, C–A, C–C, C–G, C–T, G–A, G–C, G–G, G–T, T–A, T–C, T–G, and T–T) in the previous study
(**X–Y**:A–FdU, C–FdU, G–FdU, T–FdU, FdU–A, FdU–C, FdU–G, and FdU–T) in the present study
(c)
C5FdU: 5'-d[GGACCC(FdU)GGTCC]-3'
C5FdU: 3'-d[CCTGG(FdU)CCCAGG]-5'

Fig. 1 Experimental materials used in this study. (a) Chemical structure of 5-fluorouracil (FdU). (b) Oligonucleotide sequences of the duplex DNAs, F25**X**–R25**Y**, with natural base pairs (**X**–**Y**: A–A, A–C, A–G, A–T, C–A, C–C, C–G, C–T, G–A, G–C, G–G, G–T, T–A, T–C, T–G, and T–T) used in the previous study, and with naturally modified base pairs involving FdU (**X**–**Y**: A–FdU, C–FdU, G–FdU T–FdU, FdU–A, FdU–C, FdU–G, and FdU–T) used in the present study. (c) Oligonucleotide sequence of the duplex DNA, $(C5FdU)_2$, with a self-complementary sequence involving FdU, used for X-ray crystallographic analyses in the present study.

FdU and the duplex DNAs involving FdU used in the present study are shown in Fig. 1. Experimental details are provided in the Experimental section of the ESI.†

Previously, we examined the thermal stability of a 1 μM duplex DNA series with 16 different base pairs of the form F25**X**–R25**Y** (**X**–**Y**: A–A, A–C, A–G, A–T, C–A, C–C, C–G, C–T, G–A, G–C, G–G, G–T, T–A, T–C, T–G, and T–T) (Fig. 1) in 10 mM sodium cacodylate–cacodylic acid (pH 6.8) and 100 mM $NaClO_4$, with or without $Hg(ClO_4)_2$, using UV melting. Our findings indicated that binding to Hg^{2+} specifically stabilized only the duplex DNA with the T–T base pair.[22] We also investigated the thermal stability of the 1 μM duplex DNA series of F25**X**–R25**Y** (Fig. 1) in 10 mM sodium cacodylate–cacodylic acid (pH 6.8) and 100 mM $NaNO_3$ (buffer A), with or without $AgNO_3$, using UV melting. Our findings indicated that binding to Ag^+ specifically stabilized only the duplex DNA with the C–C base pair.[30] To examine the possibility of specific binding of metal ions other than Hg^{2+} and Ag^+ to naturally modified mismatched base pairs in duplex DNA, we examined the thermal stability of a 1 μM duplex DNA series involving FdU, F25**X**–R25**Y** (**X**–**Y**: A–FdU, C–FdU, G–FdU, T–FdU, FdU–A, FdU–C, FdU–G, and FdU–T) (Fig. 1), in buffer A, with or without 1 or 2 μM metal ions (Cu^{2+}, Zn^{2+}, Cd^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Pb^{2+}, Cr^{3+}, Mn^{2+}, and Tl^+), using UV melting (Fig. 2, Table 1, and Tables S1–S8†). Without metal ions, the T_m of F25A–R25FdU (74.1 °C) was slightly higher than those of F25C–R25FdU, F25G–R25FdU, and F25T–R25FdU, whereas that of F25FdU–R25A (72.4 °C) was slightly higher than those of F25FdU–R25C, F25FdU–R25G, and F25FdU–R25T (Table 1 and Tables S1–S8†). The addition of 2 μM $Zn(NO_3)_2$, $Cd(NO_3)_2$, $Fe(NO_3)_3$, $Co(NO_3)_2$, $Ni(NO_3)_2$, $Pb(NO_3)_2$, $CrCl_3$, $MnCl_2$, and $TlNO_3$ did not significantly change the T_m of the 1 μM duplex DNA series (Tables S1–S8†). In contrast, adding 1 μM $Cu(NO_3)_2$ slightly increased the T_m of duplex DNA with the C–FdU and FdU–C base pairs by 3.8 °C and 4.7 °C, respectively (Table 1). However, the T_m of duplex DNAs with A–FdU, G–FdU, T–FdU, FdU–A, FdU–G, and FdU–T base pairs did not significantly change upon the addition of 1 μM $Cu(NO_3)_2$. These results indicated that Cu^{2+} addition significantly and specifically stabilized only the duplex DNA with C–FdU and FdU–C base pairs, forming C–Cu–FdU and FdU–Cu–C, respectively. Adding 2 μM $Cu(NO_3)_2$ also significantly increased the T_m of the duplex DNA with C–FdU and FdU–C base pairs by 5.6 °C and 6.2 °C, respectively (Table 1), which was a significantly larger increase than the T_m changes observed for other duplex DNAs (Table 1). The increase in T_m upon adding 2 μM $Cu(NO_3)_2$, denoted by ΔT_m ($+2Cu^{2+}$) (°C; 5.6 °C and 6.2 °C for C–FdU and FdU–C base pairs, respectively), was slightly larger than that upon adding 1 μM $Cu(NO_3)_2$, denoted by ΔT_m ($+Cu^{2+}$) (°C; 3.8 °C and 4.7 °C for C–FdU and FdU–C base pairs, respectively) (Table 1). The value of ΔT_m ($+2Cu^{2+}$)–ΔT_m ($+Cu^{2+}$) (°C; 1.8 °C and 1.5 °C for C–FdU and FdU–C base pairs, respectively) was significantly smaller than that of ΔT_m ($+Cu^{2+}$) (°C). These results showed that a molar ratio of $[Cu^{2+}]$/[duplex DNA] = 1 sufficiently stabilized the duplex DNA with C–FdU and FdU–C base pairs.

To examine the effect of Cu^{2+} addition on the higher-order structure of duplex DNA, we measured the CD spectra of the same 1 μM duplex DNA series involving FdU, F25**X**–R25**Y** (**X**–**Y**: A–FdU, C–FdU, G–FdU, T–FdU, FdU–A, FdU–C, FdU–G, and FdU–T) (Fig. 1), in buffer A, with or without 1 or 2 μM $Cu(NO_3)_2$, at 25 °C (Fig. S1†). The CD profile of each duplex DNA with 1 or 2 μM $Cu(NO_3)_2$ was similar to that observed without $Cu(NO_3)_2$. These results indicated no significant change in the higher-order structure of any duplex DNAs upon Cu^{2+} addition.

To investigate the detailed structure of the complex between C–FdU or FdU–C base pairs in duplex DNA and copper ions, we crystallized the duplex DNA $(C5FdU)_2$ with a self-complementary sequence involving consecutive C–FdU and FdU–C base pairs in the center, in the presence of $Cu(NO_3)_2$. The crystal structure of the complex between the $(C5FdU)_2$ duplex DNA and copper ions, forming C–Cu–FdU and FdU–Cu–C metal-mediated base pairs, was determined at a resolution of 2.5 Å (Fig. 3). The data collection and structure refinement statistics are summarized in Table S9.† Duplex DNA involving C–Cu–FdU and FdU–Cu–C metal-mediated base pairs adopted an A-form structure. The obtained structure of the complex, with a 2 : 2 binding stoichiometry of copper ions and C–FdU and FdU–C base pairs, provided insight into how copper ions bound to C–FdU and FdU–C base pairs in duplex DNA. Copper ions bound to the N3 positions of both C and FdU in the complex through linear coordination to form C–Cu–FdU and FdU–Cu–C metal-mediated base pairs (Fig. 4), indicating that copper ion binding induced deprotonation at the N3 position of FdU. Similar deprotonation reactions were observed for the formation of T–Hg–T base pairs.[25] The dis-

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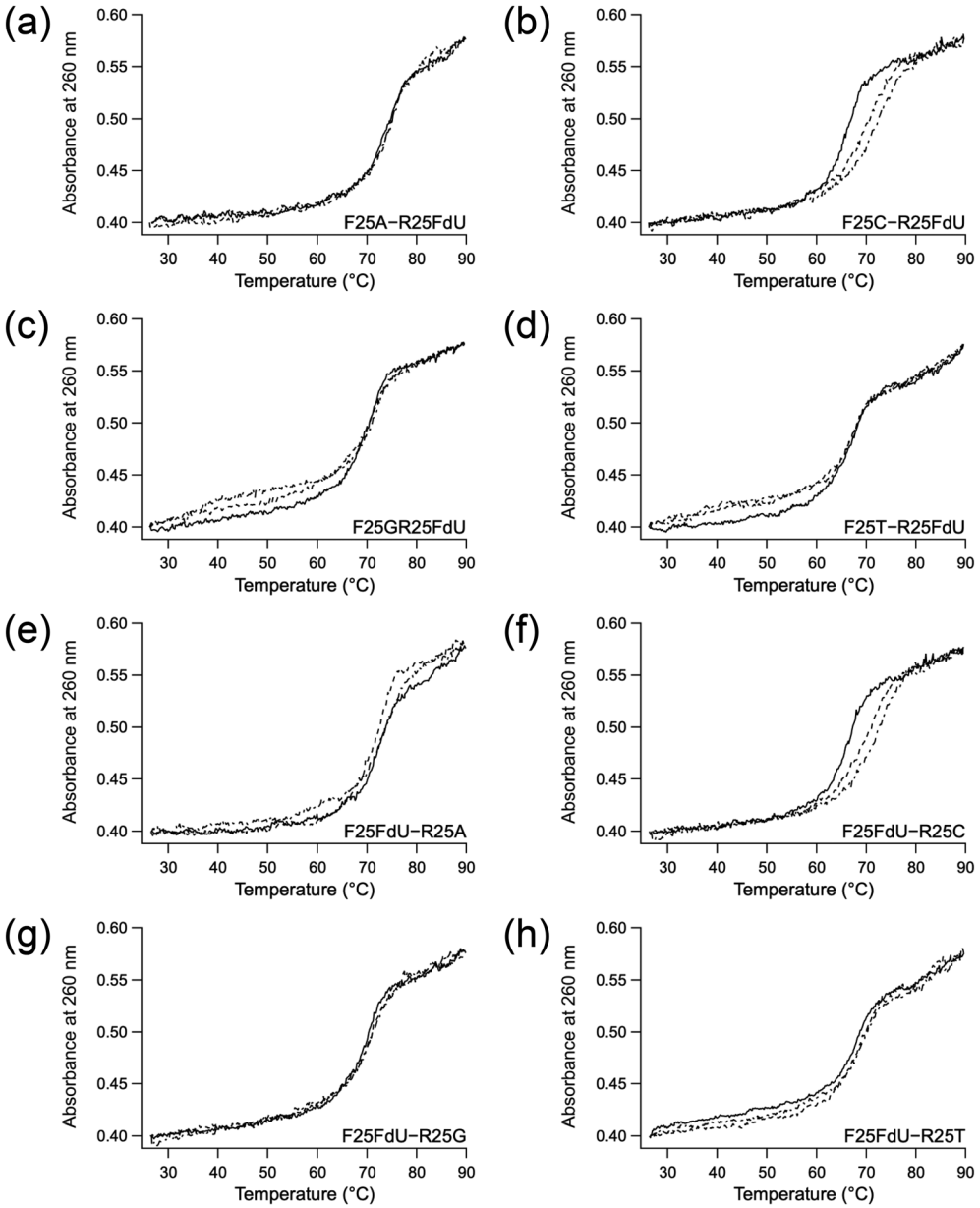

Fig. 2 UV melting profiles of duplex DNA: (a) F25A–R25FdU, (b) F25C–R25FdU, (c) F25G–R25FdU, (d) F25T–R25FdU, (e) F25FdU–R25A, (f) F25FdU–R25C, (g) F25FdU–R25G, and (h) F25FdU–R25T, with or without $Cu(NO_3)_2$. Duplex DNA (1 μM) in 10 mM sodium cacodylate–cacodylic acid (pH 6.8) and 100 mM $NaNO_3$ (buffer A), without (solid line) or with 1 μM (dotted line) or 2 μM (dashed-dotted line) $Cu(NO_3)_2$, was melted at 0.2 °C min^{-1} with detection at 260 nm. Path length was 1 cm.

Table 1 Melting temperatures (T_m) of the 1 μM duplex DNA [F25**X**–R25**Y** (**X**–**Y** = A–FdU, C–FdU, G–FdU, T–FdU, FdU–A, FdU–C, FdU–G, and FdU–T)] at pH 6.8 in 10 mM sodium cacodylate–cacodylic acid and 100 mM $NaNO_3$, with or without 1 or 2 μM $Cu(NO_3)_2$, obtained from UV melting experiments

X–Y	T_m ($-Cu^{2+}$) (°C)	T_m ($+Cu^{2+}$) (°C)	ΔT_m[a] ($+Cu^{2+}$) (°C)	T_m ($+2Cu^{2+}$) (°C)	ΔT_m[b] ($+2Cu^{2+}$) (°C)
A–FdU	74.1 ± 0.5	74.7 ± 0.4	0.6	75.1 ± 0.6	1.0
C–FdU	66.4 ± 0.4	70.2 ± 0.4	3.8	72.0 ± 0.2	5.6
G–FdU	70.9 ± 0.3	71.1 ± 0.4	0.2	71.7 ± 0.3	0.8
T–FdU	67.3 ± 0.3	67.7 ± 0.3	0.4	67.0 ± 0.6	−0.3
FdU–A	72.4 ± 0.4	72.8 ± 0.5	0.4	73.5 ± 0.2	1.1
FdU–C	66.5 ± 0.2	71.2 ± 0.5	4.7	72.7 ± 0.4	6.2
FdU–G	70.3 ± 0.4	70.6 ± 0.3	0.3	70.9 ± 0.3	0.6
FdU–T	68.2 ± 0.3	68.8 ± 0.4	0.6	69.1 ± 0.1	0.9

[a] ΔT_m ($+Cu^{2+}$) = T_m ($+Cu^{2+}$) − T_m ($-Cu^{2+}$). [b] ΔT_m ($+2Cu^{2+}$) = T_m ($+2Cu^{2+}$) − T_m ($-Cu^{2+}$).

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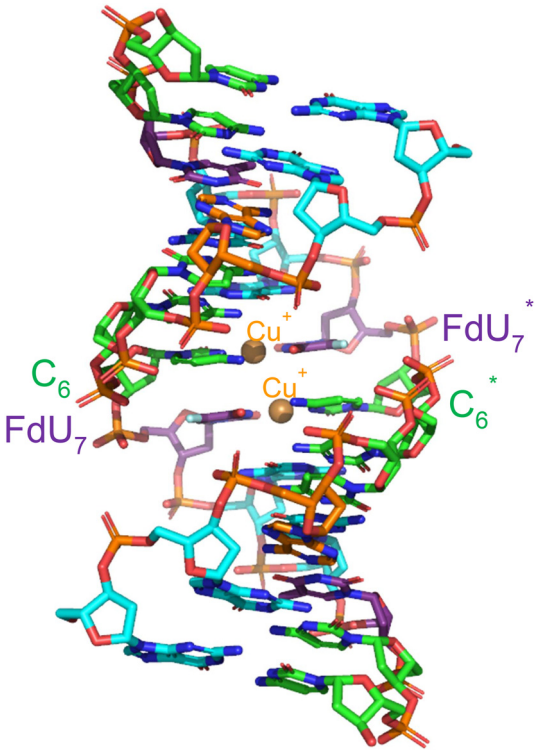

Fig. 3 Overall structure of the duplex DNA $(C5FdU)_2$ in complex with copper ions. The duplex DNA exhibits crystallographic two-fold symmetry at the center of the molecule.

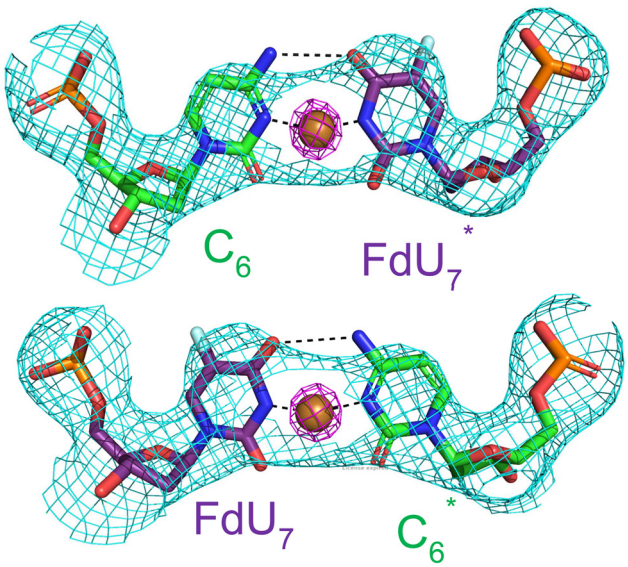

Fig. 4 Details of the copper ion-mediated C–Cu–FdU and FdU–Cu–C base pairs. The $2mF_o–DF_c$ map (cyan) and anomalous difference Fourier map (magenta) are shown, with contours at the 1σ and 15σ levels, respectively.

tances between copper ions and the N3 positions of C and FdU were 2.0 and 1.8 Å, respectively (Fig. 4). The distances were comparable in magnitude to those previously reported between Hg^{2+} and the N3 position of T in the T–Hg–T base pair (2.0 Å)[25] and between Ag^+ and the N3 position of C in the C–Ag–C base pair (2.2–2.3 Å).[31] A hydrogen bond with a distance of 3.1 Å was formed between the N4 atoms of C and the O4 atom of FdU (Fig. 4), implying its contribution to the higher stability of C–Cu–FdU and FdU–Cu–C metal-mediated base pairs by forming a stronger bonding network. The copper-ion–copper-ion distance was 3.6 Å.

When Hg^{2+} and Ag^+ specifically bind to the T–T and C–C base pairs in duplex DNA, respectively, the one-dimensional linear coordination geometries of Hg^{2+} and Ag^+ are used to form the T–Hg–T and C–Ag–C base pairs.[25,31] In the present study, the crystal structure indicated that the linear coordination geometry of the complex with monovalent Cu^+, similar to that with Hg^{2+} and Ag^+, was utilized to bind to C–FdU and FdU–C base pairs in the duplex DNA and to form C–Cu–FdU and FdU–Cu–C base pairs. This is despite the fact that divalent Cu^{2+} derived from $Cu(NO_3)_2$ in the experimental buffer typically has the potential to form nonlinear coordination geometries, such as square-planar and tetrahedral, within copper-containing complexes.[39] The electron-withdrawing ability of FdU from the 5-fluorine may alter the electron density distribution of the uracil base, and the N3-deprotonated form of FdU may be available in pH-dependent solutions.[40–42] The combination of the linear coordination geometry of the complex involving monovalent Cu^+ and the N3-deprotonated form of FdU may result in the formation of C–Cu–FdU and FdU–Cu–C base pairs, as demonstrated in this study. The *in situ* reduction of divalent Cu^{2+} to monovalent Cu^+, observed during the formation of C–Cu–FdU and FdU–Cu–C base pairs in this study, was previously reported in another case.[43] Divalent Cu^{2+} preferentially binds to the charged phosphate group and the N-7 atom of guanine in DNA.[44] Kawanishi *et al.* reported that divalent Cu^{2+} bound to guanine-rich regions of DNA may undergo *in situ* reduction to monovalent Cu^+, which subsequently reacts with H_2O_2 to form DNA-Cu^+OOH complex.[43] Further studies are necessary to reveal more details of the mechanism by which divalent Cu^{2+} with a non-linear coordination geometry in the experimental buffer binds to form C–Cu–FdU and FdU–Cu–C base pairs containing monovalent Cu^+ with a linear coordination geometry in duplex DNA.

Conclusions

Metal-mediated base pair formation, resulting from specific binding between metal ions and natural or naturally modified mismatched base pairs in duplex DNA, has potential applications in various fields,[26] including metal ($Hg^{2+}$and Ag^+) sensors, Hg^{2+} trapping, single nucleotide polymorphism detection, and DNA nanomachines (DNA tweezers, DNA walkers, and logic gates). To date, only Hg^{2+}- and Ag^+-mediated natural and naturally modified mismatched base pairs in duplex DNA have been utilized in these applications. To the best of our knowledge, no previous studies have reported the copper ion binding ability of naturally modified mismatched base pairs in

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duplex DNA. Thus, the C–Cu–FdU and FdU–Cu–C base pairs demonstrated in this study may be unique examples of metal-mediated naturally modified mismatched base pairs. The findings of this study could expand the potential of metal-mediated naturally modified mismatched base pairs in duplex DNA. The potential applications of these novel copper ion-mediated, naturally modified mismatched base pairs are expected to extend into various fields, including nanotechnology.

Data availability

The data supporting this article have been included as part of the ESI.† If any additional questions regarding experimental details arise, the corresponding author remains at the readers' disposal. The crystal structure data obtained in this article have been deposited in the Protein Data Bank (PDB) under the PDB-ID code 9KCC.

Conflicts of interest

There are no conflicts of interest to declare.

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