

Self-Assembly of Chelator-Type Nucleic Acid Mimics into a Single-Stranded Zn^{II} Coordination Polymer

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(Received April 28, 2000; CL-000407)

The synthesis of a “chelator-type” adenine mimic, which has two metal binding sites, and its Zn^{II}-assisted self-assembly into a single-stranded coordination polymer are described. The UV absorption changes of a 1 : 1 mixture of the Zn^{II} complex and a single-stranded DNA oligomer (dT)₇₀ showed the temperature-dependent hyperchromic effect in an analogous manner as thermal denaturation processes of natural DNA duplexes.

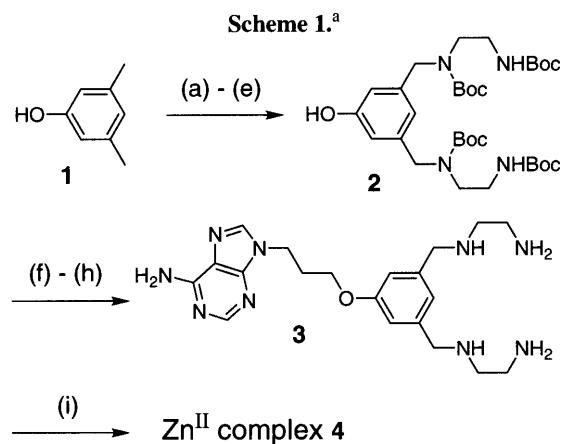
The self-assembly of noncovalently linked molecular clusters of unique building blocks has currently received considerable attention.¹ In particular, “template-directed” approaches² are becoming common and have been accepted promising for the construction of the ideally pre-designed assembly. One of the most appealing paradigms of self-assembly in biological system is sequence-specific association between two complementary nucleic acid strands, and such processes play essential roles in most genetic events. DNA oligonucleotides have been intensively used as templates for reaction control on the template such as self-replication³ and cyclization⁴ of the guest DNA components.

As an approach to novel metal-assembled systems directed to a single-stranded DNA as the template, we have synthesized a “chelator-type” adenine mimic **3** which could be built up into a single-stranded polymer **4** with the cooperative participation of metal coordination. Two metal binding sites and an adenine base moiety were introduced into compound **3** so that it can undergo strand formation by intermolecular metal coordination thereby possibly interacting with a natural DNA strand through Watson–Crick base pairing.

Compound **3** was synthesized from 3,5-dimethylphenol, **1**, according to Scheme 1. Protected ethylenediamine subunits were attached to the benzylic positions of **1** to obtain **2**. Compound **2** serves as a common intermediate for the introduction of nucleobases at the phenolic position. Here we present the synthesis of an adenine mimic **3**.⁵ The coupling reaction of compound **2** with 9-(3-chloropropyl)adenine,⁶ which was prepared from adenine and 1-bromo-3-chloropropane, was performed in DMF in the presence of *t*BuOK. The resulting product was then treated with 1 M HCl in acetic acid, followed by ion exchange column chromatography (IRA-400), to afford **3** in the acid-free form.

The adenine mimic **3** reacted with Zn^{II}(NO₃)₂ in water to form Zn^{II} complex **4**.⁷ The elemental analysis (C, H, N) of this complex was in agreement with the composition [3–Zn^{II}(OH₂)₂](NO₃)₂. The characteristic changes of ¹H NMR spectrum for **4** in D₂O were marked downfield shifts and splittings of the signals for the ethylenediamine moieties upon Zn^{II} complexation.

The molecular structure of the Zn^{II} complex **4** was charac-



^aReagents and conditions: (a) pivaloyl chloride, DMAP, (*i*Pr)₂NEt in CH₂Cl₂, rt, 1 h (98%); (b) NBS, benzoylperoxide in CCl₄, reflux, 22 h (58%); (c) NH₂CH₂CH₂NHBoc, (*i*Pr)₂NEt in CH₂Cl₂, 50 °C, 2 h (45%); (d) di-*t*-butylbiscarbonate, (*i*Pr)₂NEt in CH₂Cl₂, 35 °C, 3 h (78%); (e) 1 M NaOH in H₂O, THF, 60 °C, 6 h (100%); (f) 9-(3-chloropropyl)adenine, *t*BuOK in DMF, rt, 10 days (59%); (g) 1.0 M HCl in AcOH, rt, 1 h (82%); (h) IRA-400 (100%); (i) Zn(NO₃)₂·6H₂O in H₂O, rt, 10 days (75%).

terized by single-crystal X-ray crystallography.⁸ Each ethylenediamine moiety binds to Zn^{II} to form a *trans*-N₄-plane, and two water molecules at the axial positions complete the octahedral structure (Figure 1a). Adenine analogues **3** are intermolecularly linked together by Zn^{II} ions that provide the driving force for polymerization by imposing an octahedral coordination geometry at each site. The adenine bases are attached to the main chain through a propyl chain and an aromatic ring, pointing away from the axis of the Zn^{II} polymer (Figure 1b). Although the Zn^{II}–Zn^{II} distance of 7.718 Å is rather longer than the average distance between adjacent phosphodiester groups in the same chain of B-DNA (ca. 6 Å), molecular modeling studies indicated that this complex is structurally flexible enough for complementary binding to a single-stranded natural DNA.⁹ In contrast to DNA the coordination polymer has positive charges along the strand backbone. Therefore, this should be able to interact with negatively charged single-stranded DNA electrostatically and with hydrogen bonding through the adenine base moieties.

We then examined interactions of the Zn^{II}-assembled adenine polymer **4** with oligo (dT)₇₀ using UV absorption changes. Figure 2 shows the temperature-dependency of the absorption at 260 nm for a 1 : 1 mixture of **4** and (dT)₇₀ ([**4**] = [(dT)₇₀] = 15 μmol dm⁻³/base, 1 mM Mops buffer at pH 7.0) when the solution temperature was elevated from 0 °C to 80 °C. An absorption break was observed at 39 °C with ca. 70% hyper-

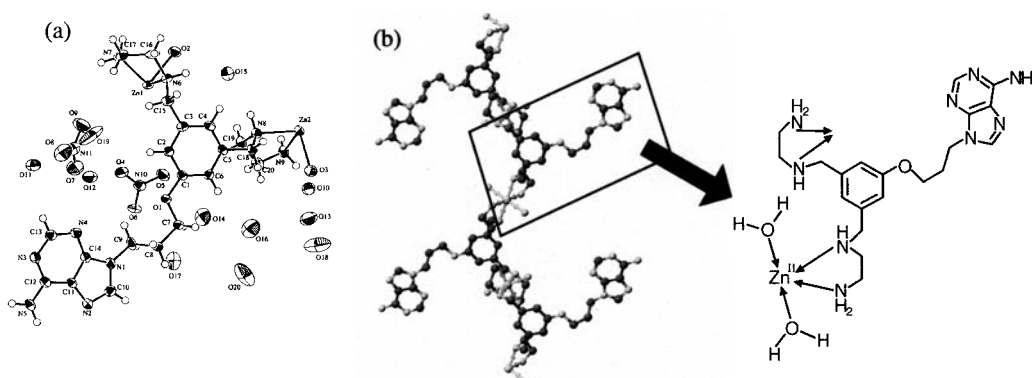


Figure 1. The crystal structure of Zn^{II} complex **4**. (a) An ORTEP view. (b) One dimensional polymeric structure.

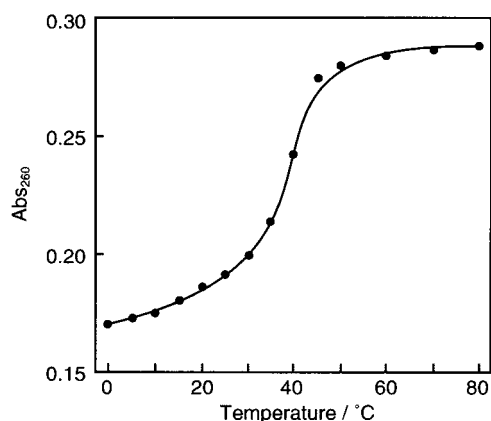


Figure 2. Temperature-dependency of the UV absorbance of a 1 : 1 mixture of Zn^{II} complex **4** and $(dT)_{70}$. $[(dT)_{70}] = [Zn^{II} \text{ complex}] = 15 \mu\text{mol dm}^{-3}/\text{base}$, Mops buffer (1.0 mM, pH 7.0).

chromicity, and almost the same curve was obtained even when the temperature was changed downwardly. This behavior is common in the naturally occurring nucleic acids. Under the same condition with a low ionic strength, the oligonucleotide $(dT)_{70}$ did not form a stable double strand with $(dA)_{70}$.¹⁰

The Zn^{II} complex **4** thus preferably associates with a natural DNA oligomer probably through electrostatic and hydrogen bonding interactions accompanied by hydrophobic effects. ¹H NMR and X-ray analytical studies are now underway to obtain a direct evidence for the hydrogen-bonded base pairing. Such artificially-designed nucleic acid components that can undergo metal-assisted assembly in a reversible fashion would provide novel molecular array systems directed to information-bearing DNA or RNA for applications not only to metallo-antisenses for gene regulation but also to molecular memory devices or molecular wires.

We thank JSPS Research Fellowships for Young Scientists (No. 7960 for AH) for financial support. Support from the Ministry of Education, Science, Sports and Culture (Grant-in-Aids for Scientific Research on Priority Areas, No. 11136255 'Metal-Assembled Complexes' and No. 706 'Dynamic Control of Stereochemistry' for MS) is gratefully acknowledged. MS is also grateful to Novartis Foundation for the Promotion of Science, Nagase Science and Technology Foundation, and Uehara Memorial Foundation for support.

References and Notes

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- The syntheses of the other three nucleobase analogues having a thymine, a guanine, or a cytosine base will be reported elsewhere.
- The use of 9-(1-bromopropyl)adenine mainly provided an intramolecularly cyclized product.
- Synthesis of Zn^{II} complex (**4**): To a solution of **3** (23 mg, 55 μmol) dissolved in distilled water (100 μL) was added 0.5 M $Zn^{II}(\text{NO}_3)_2$ aqueous solution (110 μL). The reaction mixture was filtered and the filtrate was slowly evaporated to obtain **4** as colorless prisms, which were collected and dried in vacuo for 6 h at room (25 mg, 84%). ¹H NMR (D_2O) δ : 1.91 (2H, br), 2.77 (4H, br), 2.96 (2H, br), 3.67 (4H, s), 3.99 (2H, br), 4.34 (2H, br), 6.37 (2H, s), 6.79 (1H, s), 7.88 (1H, s), 8.06 (1H, s); Anal. Calcd for $C_{20}H_{35}N_{11}O_9Zn$: C, 37.60; H, 5.52; N, 24.11%. Found: C, 37.48; H, 5.65; N, 23.87%.
- Crystal data for $C_{20}H_{35}N_{11}O_9Zn$, size = $0.20 \times 0.15 \times 0.08 \text{ mm}^3$, triclinic, space group = group $P\bar{1}$ (#2), $a = 11.915(1) \text{ \AA}$, $b = 15.182(1) \text{ \AA}$, $c = 11.3573(7) \text{ \AA}$, $\alpha = 94.207(5)^\circ$, $\beta = 96.928(5)^\circ$, $\gamma = 71.382(3)^\circ$, $V = 1931.6(3) \text{ \AA}^3$, $Z = 2$, $D_c = 1.408 \text{ g cm}^{-3}$, $T = -50.0 \text{ }^\circ\text{C}$, $\mu(\text{MoK}\alpha) = 17.20 \text{ cm}^{-1}$, $R = 0.063$, $R_w = 0.087$, 5031 unique reflections out of 7386 with $[I > 3.00\sigma(I)]$.
- Natural single-stranded DNAs can often pair flexibly with artificially synthesized nucleic acid mimics such as PNA; for instance, see P. E. Nielsen, M. Egholm, R. H. Berg, and O. Buchardt, *Science*, **254**, 1497 (1991); H. Rasmussen, J. S. Kastrup, J. N. Nielsen, J. M. Nielsen, and P. E. Nielsen, *Nat. Struct. Biol.*, **4**, 98 (1997).
- When the concentration of NaCl was increased to 100 mmol dm^{-3} the melting temperature of $(dT)_{70}$ - $(dA)_{70}$ was $59 \text{ }^\circ\text{C}$. On the other hand, no melting process was observed with a mixture of **4** and oligo $(dT)_{70}$ under the same condition.