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The conjugates of uracil–cyclen Zn(II) complexes: Synthesis, characterization, and their interaction with plasmid DNA

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Abstract—As an important nucleobase in RNA, uracil was introduced into the side chain of cyclen (1,4,7,10-tetraazacyclododecane) by using phenylene dimethylene group as bridge. The target compounds **5** were obtained in high yields. Subsequent experiments demonstrated that the uracil–cyclen conjugates can bind Zn^{2+} cation rapidly in water, and the catalytic activities of their Zn(II) complexes **6** in DNA cleavage were also studied. The results showed that Zn(II) complexes can catalyze the cleavage of supercoiled DNA (pUC 19 plasmid DNA) (Form I) to produce nicked DNA (Form II and Form III) with high selectivity. In water solution, complex **6b** may form a unique and stable supramolecular structure, which benefits the DNA cleavage process.

1. Introduction

The cleavage of DNA with high selectivity has become an invaluable tool in biology, bioorganic chemistry, and molecular biology. However, the phosphodiester bonds of DNA are very difficult to be hydrolyzed under physiological conditions.[1] A number of natural enzymes such as restriction endonucleases and topoisomerases can efficiently catalyze DNA hydrolysis.[2] The special effects of those enzymes most often depend on their active sites including metal ions, particularly Zn(II), Mg(II), and Fe(II), and their ability to act as Lewis acids.[3] In recent years, many artificial metallonucleases have been suggested as substitute for natural enzymes to cleave DNA. Among the physiologically relevant metal ions, Zn(II) is probably the best suitable metal ion for artificial metallonucleases. However, the reactivity of Zn(II) ion is somewhat lower than that of the other commonly employed transition-metal ions,[4] and this is why the examples of Zn(II)-based artificial nucleases reported to date are scarce.[5] Our goal is to develop novel Zn(II) complexes prepared from small organic ligands, and use these complexes to cleave double-strand DNA effectively. The research areas about synthetic Zn(II) complexes include following systems: (1) Barton's mononuclear Zn(II)-binding peptides tethered to rhodium complex as intercalator.[6] (2) Scrimin's binuclear Zn(II)-binding peptides' conjugate with an acridine intercalator.[7] (3) Tecilla's mononuclear Zn(II)-binding *cis–cis*-triaminocyclohexane ligands linked by an anthraquinone moiety through alkyl spacers with different lengths.[8] (4) Dinuclear macrocyclic polyamine zinc(II) complexes linked by different spacers, which was developed in our group.[9] All of above complexes have two functions: the scission part (Zn(II)) and the recognition part (intercalator).

Cyclen (1,4,7,10-tetraazacyclododecane) has strong coordination ability toward a wide range of cations, including transition metal ions and lanthanide ions.[10,11] And the complexes derived from this kind of ligands have been widely used in the fields of DNA recognition,[12,13] DNA cleavage,[14] and enzyme mimics.[15,16] In order to increase the DNA cleavage rate at low concentration of metal complex, we introduced nucleobases, which could be favorable to recognize DNA through

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Watson–Crick interaction, to the cyclen cycle. In this paper, we designed and synthesized the conjugates of cyclen and uracil bridged by rigid spacers, and applied them to the coordination with Zn(II) to form metal complexes, which may be used to cleave DNA. These complexes have some special properties: (1) Uracil, as a nucleobase, could be favorable to recognize DNA. (2) More interestingly, the metal ion in the complex could bind to the nitrogen atom of the imide of uracil group through an intramolecular or intermolecular mode, which can form a unique and stable supramolecular complex in aqueous solution. The complex that has this property displays higher activity in the DNA cleavage process than the one without the supramolecular structure. We also run ESI mass spectra to testify the special structure.

2. Experimental

2.1. General information

ESI-mass spectra data were recorded on Finnigan LCQ^{DECA} mass spectrometer. HRMS spectral data were recorded on Bruker Daltonics Bio TOF. ^1H NMR spectra were measured on a Varian INOVA-400 spectrometer and chemical shifts in ppm are reported relative to internal Me_4Si ($CDCl_3$) or 3-(trimethylsilyl) propionic-2,2,3,3-d_4 acid sodium salt (D_2O). Melting points were determined by using a micro-melting point apparatus without any corrections. 1,4,7-Tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (Boc_3-cyclen) was prepared according to the literature.[17] All chemicals and reagents were obtained commercially and used without further purification. Electrophoresis was processed by using a Biomeans Stack II-Electrophoresis system, PPSV-010. Bands were visualized by UV light and photographed followed by the estimation of the intensity of the DNA bands using a Gel Documentation System, recorded on an Olympus GRAB-it 2.0 Annotating Image Computer System. Electrophoresis grade agarose and plasmid DNA (pUC 19) were purchased from Takara Biotechnology Company.

2.2. Procedure of DNA cleavage experiments

The preparation of Zn(II) complexes **6** is described as follows: To the water solutions of the cyclen–uracil conjugates **5a** and **5b** was added 1 equiv of $Zn(ClO_4)_2{\cdot}7H_2O$ as water solution, and the pH was controlled at 8.0 by addition of NaOH solution. DNA cleavage experiments were performed as follows: supercoiled pUC 19 DNA (10 μL, 0.025 μg/μL) with certain concentration of vitamin C (V_c, if needed) in 100 mM Tris–HCl buffer was treated with complexes **6**, followed by dilution with the Tris–HCl buffer to a total volume of 35 μL. The samples were then incubated at 37 °C and loaded on a 1% agarose gel containing 1.0 μg/μL ethidium bromide. Electrophoresis was carried out at 40 V for 30 min in TAE buffer. Bands were visualized by UV light and photographed followed by the estimation of the intensity of the DNA bands using a Gel Documentation System.

2.3. Synthesis of uracil–cyclen conjugates

2.3.1. 1-[4′-(Bromomethyl)benzyl]-4,7,10-tris(*tert*-butoxycarbonyl)-1,4,7,10-tetraazacyclododecane (3a). Compound **3** was prepared as previously reported.[18] Under N_2 atmosphere, to a solution of 1,4-dibromomethylene benzene (1.03 g, 4.00 mmol) and Na_2CO_3 (0.25 g, 2.17 mmol) in 50 mL of dry CH_3CN was slowly added 1,4,7-tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane **1** (0.50 g, 1.06 mmol) under stirring. The reaction was stirred at 80 °C for 72 h. The insoluble inorganic salt was then filtered off and the filtrate was concentrated in vacuo. The residue was dissolved in $CHCl_3$ and then purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1:4) and obtained colorless amorphous solid (yield, 68.9%). Mp: 69–71 °C. ESI-MS: m/z = 757.5 $(M+Na)^+$.

2.3.2. 1-[3′-(Bromomethyl)benzyl]-4,7,10-tris(*tert*-butoxycarbonyl)-1,4,7,10-tetraazacyclododecane (3b). The synthetic method of **3b** was the same as that of **3a** except using 1,3-dibromomethylene benzene as reactant. Colorless amorphous solid was obtained (yield 73.5%). Eluent: EtOAc/petroleum ether = 1:4. Mp: 83–84 °C. ESI-MS: m/z = 766.3 $(M+Na)^+$.

2.3.3. 1-[4′-(1″-Uracilmethyl)benzyl]-4,7,10-tris(*tert*-butoxycarbonyl)-1,4,7,10-tetraazacyclododecane (4a). NaH (40 mg, 1 mmol) was added to a suspension of uracil (2.2 mmol, 244.2 mg) and KI (60 mg, catalytic amount) in dry, degassed DMSO and the mixture was stirred for 0.5 h at 50 °C under N_2 atmosphere. A solution of **3a** (2 mmol, 1.37 g) in dry DMSO was added slowly to this mixture and the reaction mixture was then stirred at 60 °C overnight. Water was added and the solution was extracted with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4 and then concentrated in vacuo below 40 °C to give crude product. The resulting crude product was purified by silica gel chromatography (methanol/chloroform = 1:8) to afford colorless amorphous solid **4a** (yield: 80%). Mp: 73–75 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.45–1.47 (m, 27H, $OC(CH_3)_3$), 2.63 (s, 4H, CH_2-cyclen), 3.27–3.73 (m, 14H, CH_2NCH_2cyclen–CH_2Ph), 4.88 (s, 2H, Ph–CH_2–uracil), 5.57–5.69 (d, 1H, $H_{(5)}$ in uracil), 7.12–7.14 (d, $H_{(6)}$in uracil), 7.14–7.28 (m, 4H, PhH); HRMS (ESI) calcd for $C_{35}H_{54}N_6O_8Na$ $[M+Na]^+$: m/z = 709.3895. Found: 709.3872.

2.3.4. 1-[3′-(1″-Uracilmethyl)benzyl]-4,7,10-tris(*tert*-butoxycarbonyl)-1,4,7,10-tetraazacyclododecane (4b). The synthetic method of **4b** was the same as that of **4a** except using **3b** as reactant. Colorless amorphous solid was obtained (yield 78.7%). Mp: 64–66 °C, ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.42–1.48 (m, 27H, $OC(CH_3)_3$), 2.63 (s, 4H, CH_2-cyclen), 3.26–3.72 (m, 14H, CH_2NCH_2cyclen–CH_2Ph), 4.88 (s, 2H, Ph–CH_2–uracil), 5.68–5.70 (d, 1H, $H_{(5)}$ in uracil, J = 0.8 Hz), 7.31–7.33 (d, $H_{(6)}$in uracil), 7.17–7.33 (m, 4H, PhH). HRMS (ESI) calcd for $C_{35}H_{54}N_6O_8Na$ $[M+Na]^+$: m/z = 709.3895. Found: 709.3891.

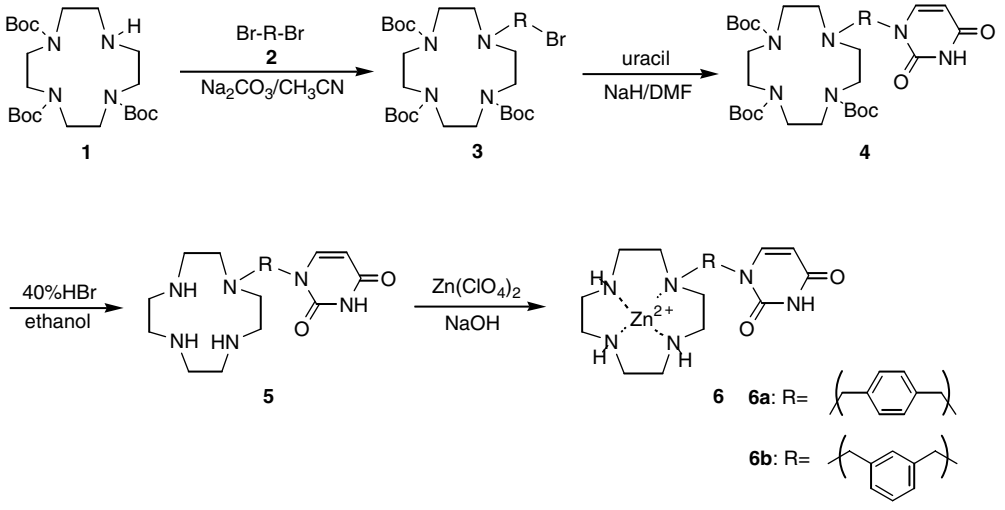
2.3.5. 1-[4′-(1″-Uracilmethyl)benzyl]-1,4,7,10-tetraazacyclododecane tetrahydrobromide (5a). To a solution of **4a** (0.709 g, 1.0 mmol) in dry EtOH (5 mL) at 0 °C, 40%

aqueous HBr (1 mL) was added slowly. After stirring overnight at room temperature, the reaction mixture was concentrated in vacuo below 40 °C to give crude product. The resulting crude product was recrystallized from EtOH/40% aqueous HBr to afford **5a**·4HBr as white powder (yield, 78%). Mp: 236–238 °C. ^{1}H NMR (D_2O, 400 MHz) δ: 2.99–3.29 (m, 16H, NCH_2CH_2N), 3.93 (cyclen–CH_2Ph), 5.05 (s, 2H, Ph–CH_2–uracil), 5.91–5.93 (d, 1H, $H_{(5)}$ in uracil, J = 8 Hz), 7.80–7.82 (d, $H_{(6)}$ in uracil, J = 8 Hz), 7.43–7.48 (m, 4H, PhH). HRMS (ESI) calcd for $C_{20}H_{31}N_6O_2$ $[M+H]^+$: m/z = 387.2503. Found: 387.2503.

2.3.6. 1-[3′-(1″-Uracilmethyl)benzyl]-1,4,7,10-tetraazacyclododecane tetrahydrobromide (5b). The synthetic method of **5b** was the same as that of **5a** except using **4b** as reactant. White powder was obtained (yield 73.3%). Mp: 190–191 °C. ^{1}H NMR (D_2O, 400 MHz) δ: 2.93–3.27 (m, 16H, NCH_2CH_2N), 3.89 (cyclen–CH_2Ph), 4.88 (s, 2H, Ph–CH_2–uracil), 5.67–5.69 (d, 1H, $H_{(5)}$ in uracil, J = 12 Hz), 7.37–7.53 (m, 4H, PhH), 7.82–7.84 (d, $H_{(6)}$in uracil, J = 8 Hz). HRMS (ESI) calcd for $C_{20}H_{31}N_6O_2$ $[M+H]^+$: m/z = 387.2503. Found: 387.2516.

2.3.7. 1-[4′-(1″-Uracilmethyl)benzyl]-1,4,7,10-tetraazacyclododecane zinc perchlorate (6a). The hydrobromide salt of **5a** (0.721 g, 1.0 mmol) was dissolved in 5 mL of water. After adjusting aqueous solution to alkaline (pH $\geqslant$ 8), $Zn(ClO_4)_2\cdot 6H_2O$ (0.408 g, 1.1 mmol) in EtOH (5 mL) was added. The mixture was stirred overnight at room temperature. The solution was gradually concentrated to give a white powder solid **6a** in 88.3% yield. Mp: >300 °C. ^{1}H NMR (D_2O, 400 MHz) δ: 2.86–3.12 (m, 16H, NCH_2CH_2N), 3.73 (cyclen-CH_2–Ph), 5.10 (s, 2H, Ph–CH_2–uracil), 5.78–5.83 (d, 1H, $H_{(5)}$ in uracil, J = 8 Hz), 7.68–7.80 (d, $H_{(6)}$ in uracil, J = 8 Hz), 7.36–7.42 (m, 4H, Ph). ESI-MS (m/z): 449.0 ($M-H^+$).

2.3.8. 1-[3′-(1″-Uracilmethyl)benzyl]-1,4,7,10-tetraazacyclododecane zinc perchlorate (6b). White powder was obtained (yield 88.5%). Mp: >300 °C, ^{1}H NMR (D_2O, 400 MHz) δ: 2.83–3.20 (m, 16H, NCH_2CH_2N), 3.69 (cyclen–CH_2–Ph), 4.82 (s, 2H, Ph–CH_2–uracil), 5.61–5.72 (d, 1H, $H_{(5)}$ in uracil, J = 12 Hz), 7.35–7.58 (m, 4H, Ph), 7.80–7.94 (d, $H_{(6)}$ in uracil, J = 8 Hz). ESI-MS (m/z): 451.2 $(M+H)^+$.



Scheme 1. The synthetic route of uracil–cyclen conjugates and their Zn(II) complexes.

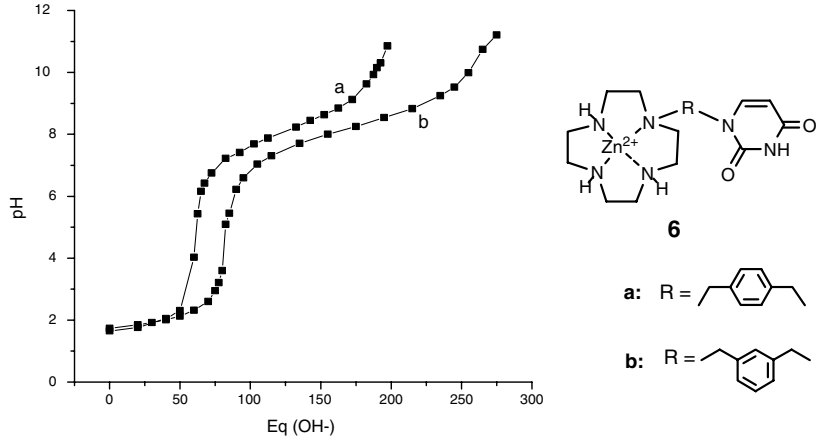


Figure 1. Typical pH titration curves of (a) 0.286 mM **6a**, (b) 0.286 mM **6b**. Conditions: 25 °C, I = 0.1 ($NaNO_3$), where Eq (OH^-) is the number of equivalents of base added.

3. Results and discussion

3.1. Synthesis of the uracil–cyclen conjugates and their Zn(II) complexes

The synthetic routes of target uracil–cyclen compounds and their Zn(II) complexes are shown in Scheme 1. The uracil–cyclen conjugate ligands **4a** and **4b** were synthesized via the reaction of uracil and 1-bromomethylbenzyl-4,7,10-tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane **3**, which were obtained by reacting 1,4,7-tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (Boc_3-cyclen) **1** with dibromomethyl (1,4- for **a** and 1,3- for **b**) benzene **2**. The Boc-protective groups were moved by adding 40% HBr aqueous solution. The cyclen–uracil Zn(II) complexes **6a** and **6b** were prepared through the reaction of **5** with zinc perchlorate.[19] The new compounds **4**–**6** were confirmed by ^1H NMR and HRMS analysis.

3.2. Potentiometric studies of 6a and 6b

The protonation was determined by potentiometric pH titration against 0.1 M NaOH with $I = 0.10$ ($NaNO_3$) at 25 °C. A typical pH titration curve is shown in Figure 1, which gave three inflections for complexes **6a** and **6b**. The first inflection can be assigned to the deprotonation of the three protons at $0 < pH < 3$, the second pH is the deprotonation of Zn(II)-bound waters at pH 7.8; the third is the deprotonation of $N^-(3)$ on uracil in complexes **6a** and **6b** at pH 9.5 (just as Scheme 2).

3.3. Interaction between complexes 6 and plasmid DNA

The activities of complexes **6a** and **6b** with pUC 19 supercoiled DNA were studied. Plasmid pUC 19 DNA was used as substrate. The DNA cleavage abilities of Zn(II) complexes were initially studied by monitoring the conditions of catalytic transforming of supercoiled plasmid (Form I) to open-circular form (Form II) and linear form (Form III). The amounts of the strands were measured by agarose gel electrophoresis.

First, we choose complex **6a** to optimize the conditions of DNA cleavage. Figure 2A–D shows the effects of pH value, vitamin C (V_c) concentration, complex

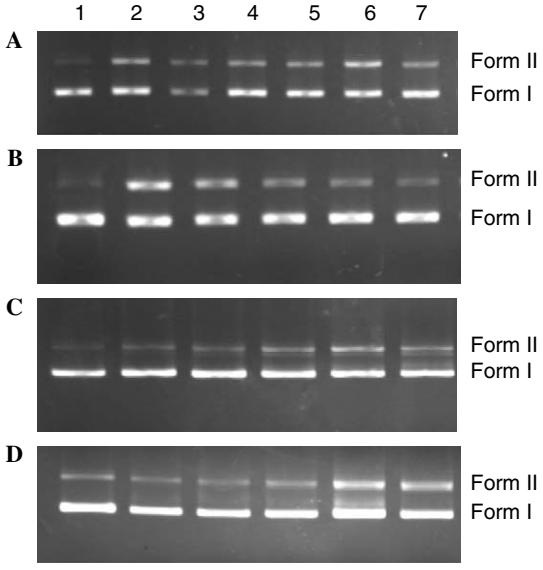
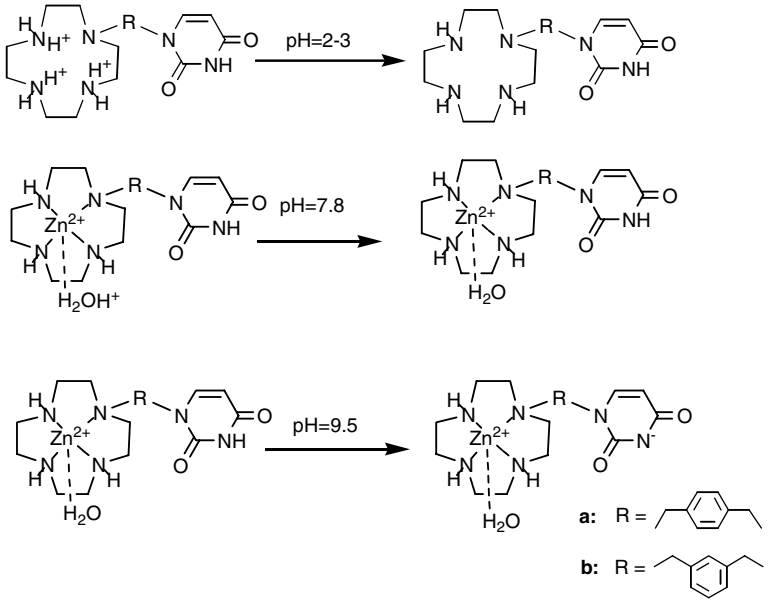


Figure 2. Agarose gel electrophoresis of cleavage reaction of pUC 19 (DNA) (7 μg/mL) in Tris–HCl buffer (100 mM, pH 8.0) at 37 °C. (A) By different pH value. Scission condition: [**6a**] = 5.74 μM, time = 3 h, [V_c] = 0.05 mM. Lane 1: DNA control; Lanes 2–7: pH 6.0, 6.5, 7.0, 7.5, 8.0, and 9.0. (B) By different V_c concentrations. Scission condition: [**6a**] = 5.74 μM, time = 3 h. Lane 1: DNA control; lanes 2–6: [V_c] = 0.7, 0.3, 0.1, 0.05, 0.025 mM. (C) By different concentration of complex **6a**. Scission condition: time = 3 h, [V_c] = 0.05 mM. Lane 1: DNA control; lanes 2–6: [**6a**] = 0.82, 2.45, 4.10, 5.74, and 9.02 μM. (D) By different cleavage time. Scission condition: [**6a**] = 5.74 μM, [V_c] = 0.05 mM. Lane 1: DNA control; lanes 2–7: time = 10, 30, 60, 120, and 180 min.



Scheme 2. Deprotonation of complexes **6**.

concentration, and cleavage time, respectively. Cleavage of DNA could be processed under physiological conditions by using very low complex concentration (at μM grade, Fig. 2C) in short time (Fig. 2D) associated with high selectivity (Form III did not appear). Figure 3 shows the quantitation of % plasmid relaxation relative to plasmid DNA per lane in Figure 2. It is obvious that Form II increased after DNA cleavage associates with the increasing of the concentration of V_c or complex. But interestingly, when we enhanced the complex concentration from 5.74 μM to 9.02 μM, the amount of Form II reduced sharply. This may be due to that Form I might be more liable to be cleaved to fragment (Form III) under high concentration of complex **6a**. In the DNA cleavage, V_c was used as reducing agent to prevent the oxidation caused by oxygen in air. Figure 2B shows that without the use of V_c, DNA could not be cleaved smoothly. According to the results, the DNA cleavage could be processed under the optimized conditions as below: pH 8.0, [complex] = 4.10 μM, reaction time = 30 min, [V_c] = 0.05 mM, and using Tris–HCl as buffer.

Then both of the complexes **6a** and **6b** were applied to the DNA cleavage. Figure 4 shows that the Zn(II) uracil–cyclen complexes **6a** and **6b** as chemical nucleases can catalyze the cleavage of plasmid DNA (pUC19) more efficiently than the zinc–cyclen complex (lanes 2–4). The results displayed that cyclen–Zn(II) at the same concentration (5.74 μM) did not result in any detectable hydrolysis, but efficient hydrolysis of plasmid DNA in the presence of **6a** and **6b** was observed. Electrophoresis and densitometry results indicated that single cleavage of the supercoiled form yielded 43.6%, 78.9% nicked form by **6a** and **6b**, respectively (Fig. 4b). In contrast, hydrolysis of supercoiled form in the presence of cyclen–Zn(II) could only give 24% yield (equal to the DNA control). Compound **6b** is better catalyst for DNA cleavage than **6a**. The data suggested that the structures of the complexes, in particular the nature of bridging groups between cyclen and uracil, play an important role in the cleavage reaction. Additionally, **6a** and **6b** could cleave DNA (pUC19) into Form II without the use of V_c, the yields are almost equal to the ones of the experiments using

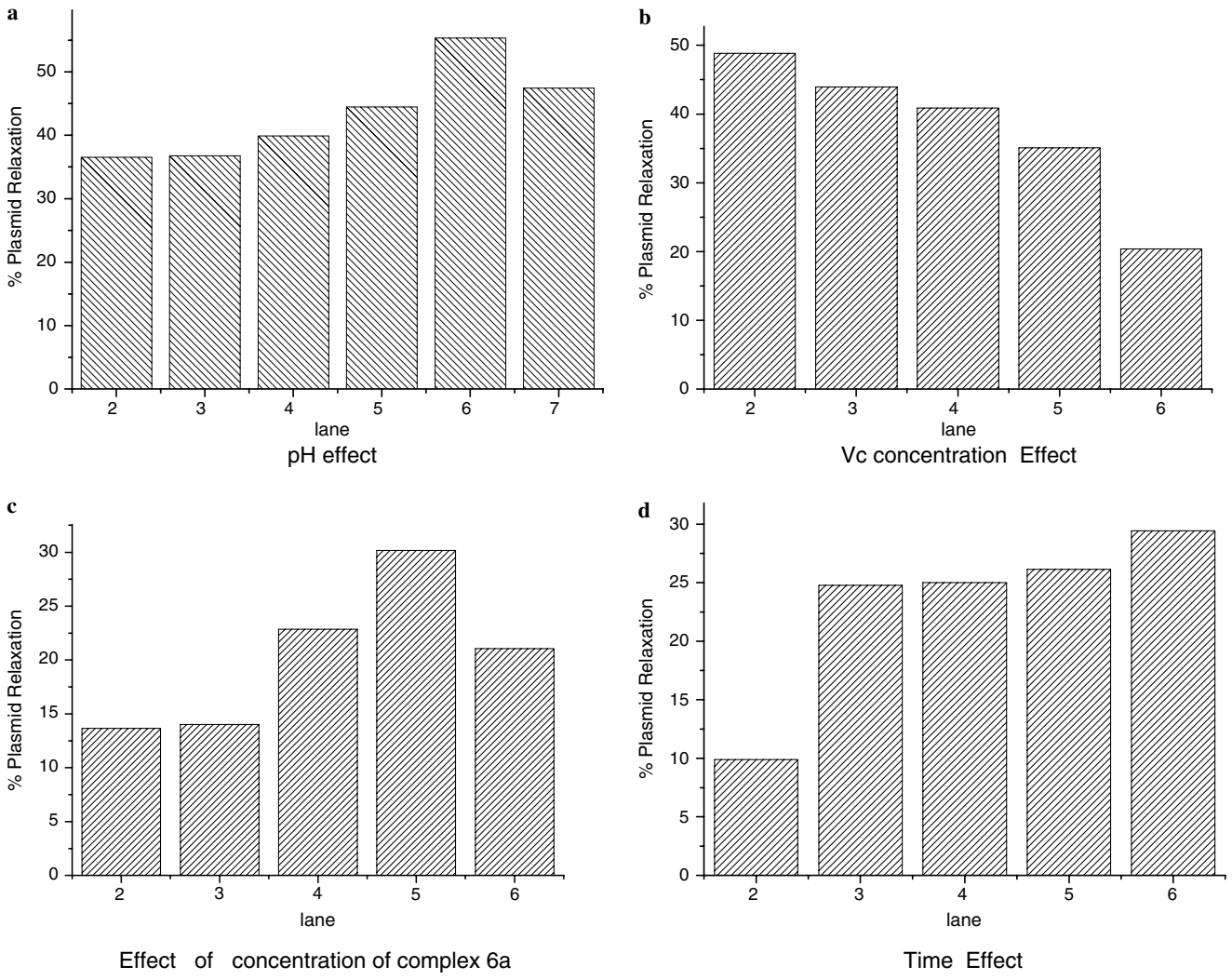


Figure 3. Quantitation of % plasmid relaxation relative to plasmid DNA per lane in Figure 2.

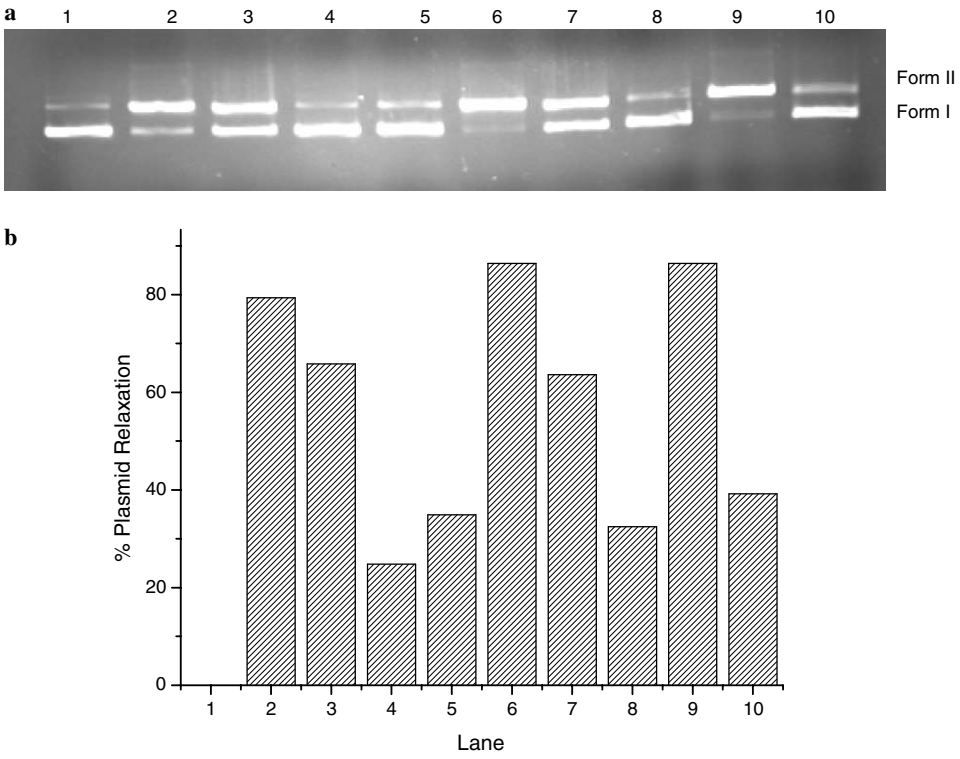


Figure 4. (a) Agarose gel electrophoresis of cleavage reaction of pUC 19 DNA (7 μg/mL) in Tris–HCl buffer (100 mM, pH 8.0) at 37 °C for 3 h. Lane 1: DNA control; lane 2: **6b** + V_c; lane 3: **6a** + V_c; lane 4: cyclen–Zn^{2+} + V_c; lane 5: V_c; lane 6: **6b** + V_c (parallel experiment); lane 7: **6a** + V_c (parallel experiment); lane 8: cyclen–Zn^{2+} + V_c (parallel experiment); lane 9: only **6b**; lane 10: only **6a**. (b) Quantitation of % plasmid relaxation relative to plasmid DNA per lane.

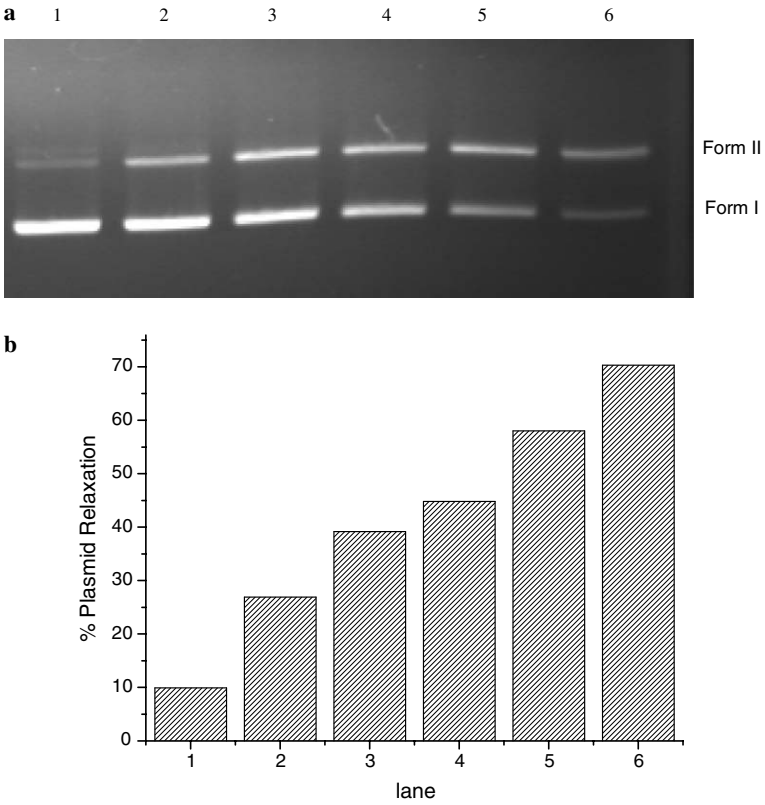


Figure 5. Effect of concentration of complex **6b** on the cleavage reaction of pUC 19 (DNA) (7 μg/mL) in Tris–HCl buffer (100 mM, pH 8.0) at 37 °C for 3 h. (a) Agarose gel electrophoresis diagram: lane 1: DNA control; lanes 2–6: **[6b]** = 0.82, 2.45, 4.10, 5.74, and 9.02 μM. (b) Quantitation of % plasmid relaxation relative to plasmid DNA per lane.

V_c as reductant (lanes 9 and 10). Our subsequent efforts focused on the reactivity of complex **6b**.

The cleavage of DNA by different concentrations of complex **6b** was also studied (Fig. 5). The amount of nicked DNA (Form II) observed in agarose gel electrophoresis diagram increased associated with the increase of the concentration of complex **6b** in the reaction system. Increasing the concentration of **6b** in the order of 0.82, 2.45, 4.10, 5.74, 9.02 μM, the nicked DNA (Form II) was obtained with 9.92%, 26.93%, 39.36%, 44.82%, 58.03%, and 70.34% yields, respectively (Fig. 5b). Like **6a**, Form I can be efficiently cleaved to fragment (Form III) within 30 min (lane 6) when we increased the concentration of **6b** to 9.02 μM. For all experiments using **6b** as catalyst, the conversion of Form I was higher than the reactions under same conditions catalyzed by **6a**.

3.4. Mass study of 6a and 6b

ESI-mass (positive) spectra of **6a** and **6b** were studied to analyze the detail structures of the complexes. As shown above, in the condition of pH 8.0, the cleavage effect of **6** is the highest, so we choose pH 8.0 as ESI-mass experiment condition. Uracil, which has an imide part, can give lone pair electron on N atom and combine to

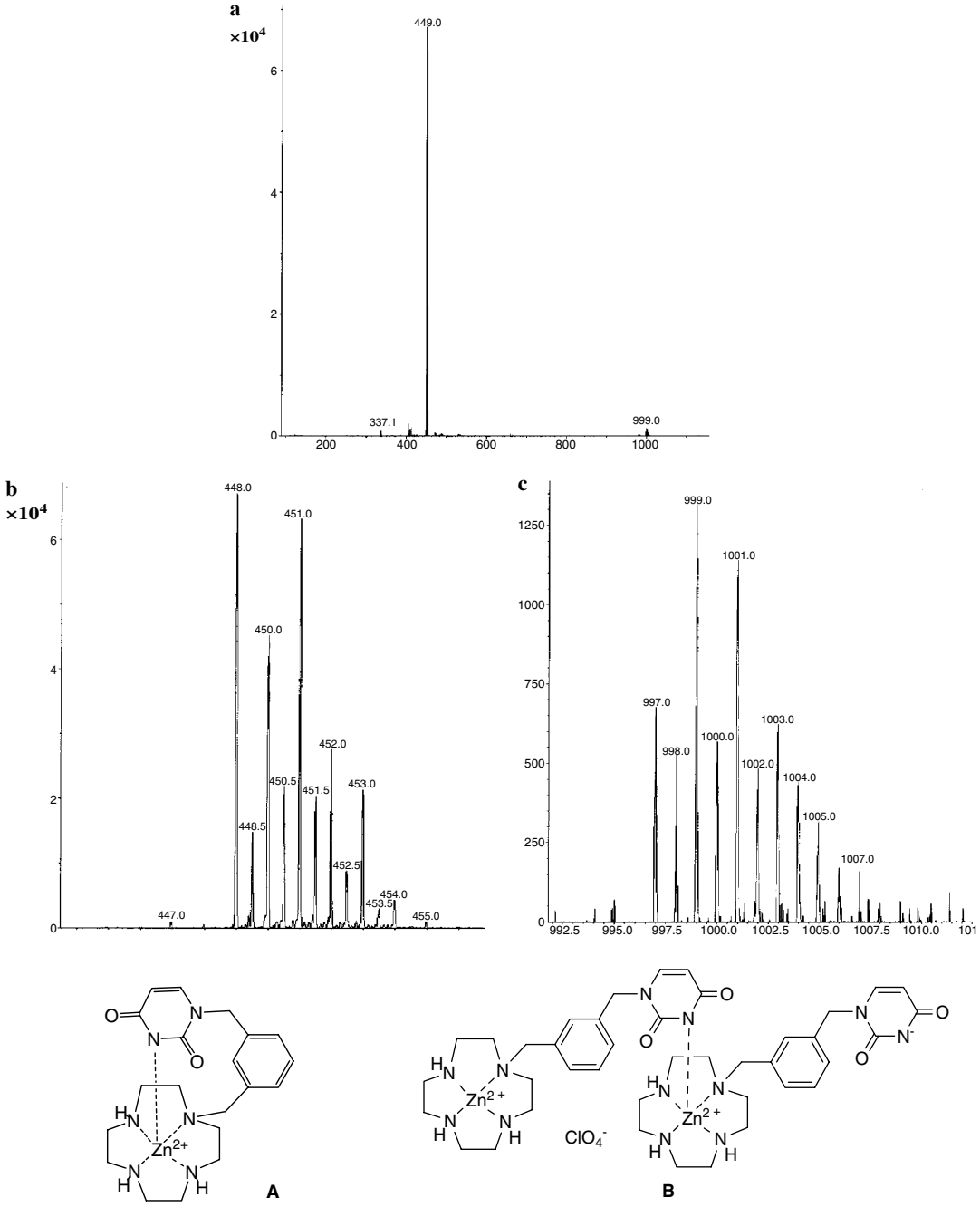


Figure 6. ESI-mass spectra of **6b**. (a) Full mass spectra; (b) M^+; (c) $2M^+ + ClO_4^-$.

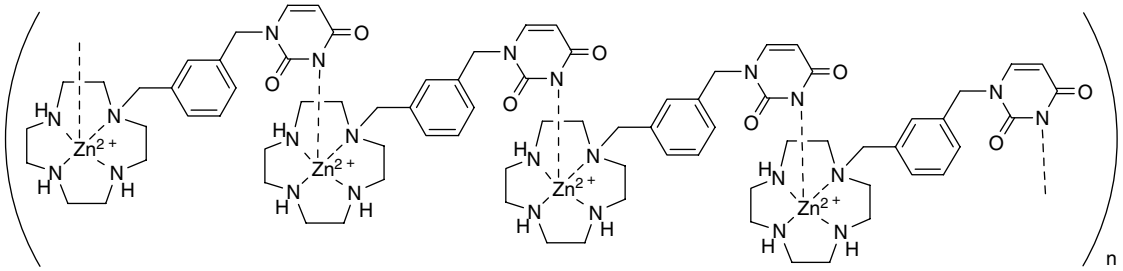


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Figure 7. Supposed supramolecular structure assembled by **6b**.

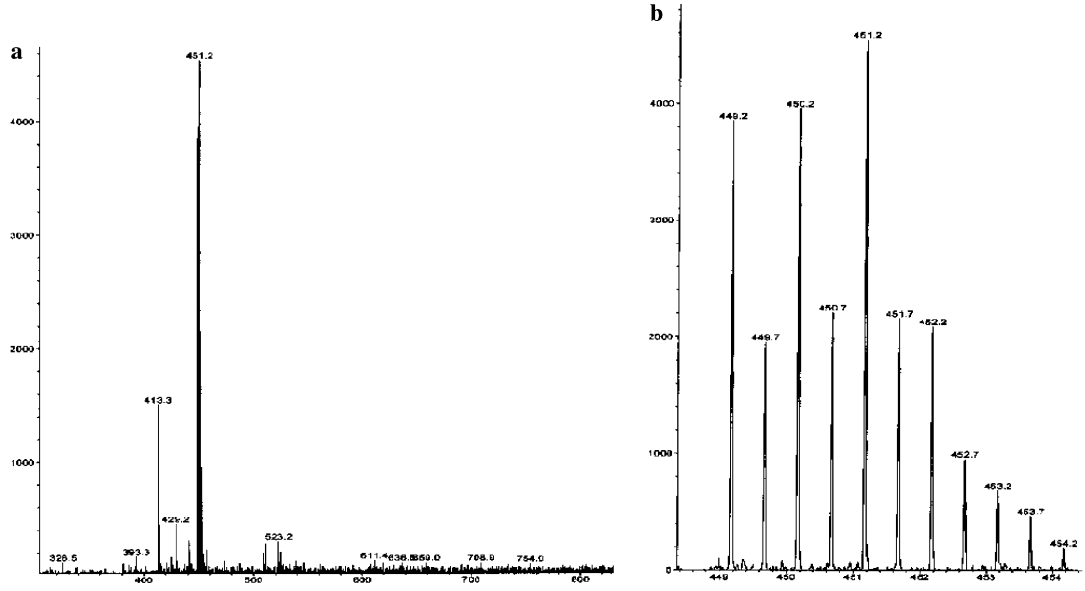

Figure 8. ESI-mass spectra of **6a**. (a) Full mass spectra; (b) M^+.

Zn(II). As results, compound **A** could be formed through intramolecular recognition mode and compound **B** could be formed by an intermolecular mode. Figure 6 gives the ESI-mass spectra of **6b**, *m/e* 449.0 and 999.0 indicate the mass of compounds **A** and **B**, respectively. We supposed that a supramolecular complex like **7** might be formed through the Zn(II)–uracil interaction (Fig. 7).

The existence of dimer or polynuclear complexes may enhance the DNA cleavage ability. Figure 8 shows the ESI-mass spectra of **6a**. The peak at *m/e* = 451.3 indicates the mass of $M+H^+$ of **6a**. Unlike **6b**, the Zn(II) complex dimer or polymer of **6a** cannot be observed in the ESI-mass spectra. This may be due to that in **6a**, the spacer does not have a right angle to form a supramolecular structure like **7**, which might be the reason for that the cleavage ability of **6b** is much better than that of **6a**. The existence of polynuclear Zn(II) complex in **6b** stands a good chance to be favorable to cleave DNA.

4. Conclusion

In this paper, we first designed and synthesized the conjugate ligands of cyclen–uracil, and correlated macrocyclic polyamine Zn(II) complexes of **6a** and **6b** were also prepared. The results of DNA cleavage show that these Zn(II) complexes are able to accelerate the plasmid DNA cleavage dramatically. The complex with 1,3-phenylenedimethylene as bridge (**6b**) is better for DNA cleavage than the one with 1, 4-phenylenedimethylene as bridge (**6a**). In complex **6b**, the metal ion in the complex could bind to the nitrogen atom of the imide of uracil group intramolecularly or intermolecularly, which can form a unique reversible and stable supramolecular complex in aqueous solution. The complex that has this property displays higher activity in the DNA cleavage process than the one without the supramolecular structure. ESI mass spectra were studied to testify the special structure. From the MS of **6b**, we can clearly find the peak belongs to the dimer. As a result, cyclen–uracil Zn(II) complexes as chemical nucleases are able to accelerate the plasmid DNA cleavage at low concentration within shorter time, and because of the uracil part, some interesting supramolecular structures might be formed in water solution.

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