Molecular Recognition of Bases and Nucleosides by Mono-substituted Mononuclear Complexes of 1,4,7,10-Tetraaza-cyclododecane[†]

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The mononuclear macrocyclic polyamine metal complexes **5a—5e** have been shown to form stable 1:1 complexes with bases and nucleosides. Their binding constants (*K*) were determined by UV-visible spectrometric titration. The results show that recognition ability of the complexes **5a—5e** for uracil, U (Uridine), dT (Thymidine) is higher than that for the other bases or nucleosides (such as Cytidine, Guanosine, Adenosine). The metal ion also plays an important role for the recognition ability of complexes.

Keywords   macrocyclic polyamines, mononuclear complexes, bases, nucleosides, recognition

Introduction

The molecular recognition with strict complementarity and preorganization is on the basis of supramolecular combination.[1] Whether the selectivity or the orientation in the process of molecular recognition depends on the nature of supramolecular combination. It is well known that the selective recognition of bases and nucleosides plays a part in transmission and transcription of information in the life action. Making use of it in designing special molecules enables us to study the recognition mechanism, the relationship of recognition action forces and the structure between receptors and substrates. These studies could not only help to understand the relevant chemical phenomena in the life system, but also guide to design the novel medicament based on the nuclear acids.[2-9] Recently the molecular recognition by macrocyclic polyamine metal complexes catches people's eyes due to its potential applications in mimic enzymes, host-guest complexes, molecular self-assemblies, selective catalysis and biological relevance.[10-20] The catalytic efficiency of macrocyclic polyamine compounds mainly depends on the selective recognition to the substrate in initial process.

However our interest has been focused on the synthesis and property of tetraaza-cyclododecane macrocyclic polyamine.[21-23] As shown in Scheme 1, the syntheses of some novel tetraaza-cyclododecane macrocyclic polyamine complexes and the study of their selective recognition for the bases and the nucleosides are reported herein.

The binding constants (*K*) of macrocyclic polyamine complex receptors with bases and nucleosides were determined on the UV spectrometry in water [(303.2 ± 0.1) K, pH = 7.50 (*I* = 0.1, NaNO₃)]. It shows 1:1 of complex formation by the modified Hildbrand-Benesi equation.[24,25] The results show that recognition ability of the complexes **5a—5e** for uracil, U (Uridine), dT (Thymidine) is higher than for the other bases [such as C (Cytidine), G (Guanosine), A (Adenosine)]. The metal ion also plays an important role for the recognition ability of complexes.

Results and discussion

*UV spectrophotometric titration of **5** with bases and nucleosides*

The molecular recognition was investigated by UV spectrophotometric titration of host (6.67 μmol·L^{-1}) with bases and nucleosides (1.67—6.67 μmol·L^{-1}) at pH = 7.50, 30 ℃ with *I* = 0.1 (NaNO₃). The binding constants (*K*) and the free energy change ($-\Delta G$) are summarized in Table 1 and Table 2.

As can be seen from Table 1, the bases including purines and pyrimidines are able to be efficiently recognized by mononuclear macrocyclic polyamine Zn^{2+} complex **5**. The result also shows that metal ion is important for molecular recognition of guest. The variant metal ion may alter the recognition ability of the macrocyclic
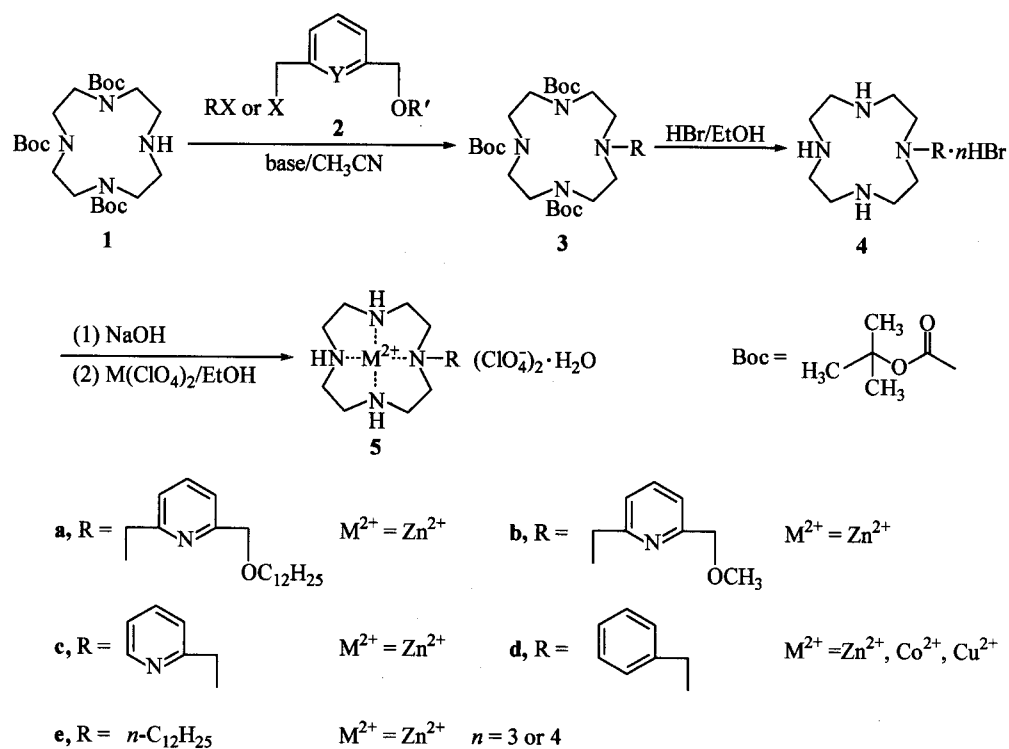
Scheme 1

Table 1 Binding constants (K), the Gibbs free energy change$(-\Delta G)$ for mononuclear macrocyclic polyamines metal complexes **5a—5e** and bases

Entry	Host	Guest	K (L·mol^{-1})	$-\Delta G$ (kJ·mol^{-1})	log K
1	**5a**	Uracil	29959	25.98	4.477
2	**5b**	Uracil	2571.9	19.79	3.410
3	**5c**	Uracil	35000	26.37	4.544
4	**5d**-Zn(II)	Uracil	35101	26.38	4.545
5	**5d**-Cu(II)	Uracil	1991	19.15	3.299
6	**5d**-Co(II)	Uracil	1688.8	18.73	3.228
7	**5e**	Uracil	3487.4	20.56	3.544
8	**5a**	5-Hydroxymethyluracil	4707.8	21.32	3.673
9	**5b**	5-Hydroxymethyluracil	4536.7	21.22	3.657
10	**5c**	5-Hydroxymethyluracil	6252	22.03	3.796
11	**5d**-Zn(II)	5-Hydroxymethyluracil	8212.5	22.72	3.915
12	**5d**-Cu(II)	5-Hydroxymethyluracil	3166.4	20.32	3.501
13	**5d**-Co(II)	5-Hydroxymethyluracil	1300	18.07	3.114
14	**5e**	5-Hydroxymethyluracil	6198.4	22.01	3.792
15	**5a**	Cytosine	3488.6	20.56	3.543
16	**5b**	Cytosine	4774.4	21.35	3.679
17	**5c**	Cytosine	1363.3	18.19	3.135
18	**5d**-Zn(II)	Cytosine	4543.7	21.23	3.657
19	**5d**-Cu(II)	Cytosine	599.2	16.12	2.778
20	**5d**-Co(II)	Cytosine	679.1	16.44	2.832
21	**5e**	Cytosine	3550.7	20.60	3.550
22	**5a**	Adenine	4296	21.08	3.633
23	**5b**	Adenine	3627.5	20.66	3.560
24	**5c**	Adenine	4365.9	21.13	3.640
25	**5d**-Zn(II)	Adenine	6551.4	22.19	3.823
26	**5d**-Cu(II)	Adenine	1462.3	18.37	3.165

Continued

Entry	Host	Guest	K (L·mol^{-1})	$-\Delta G$ (kJ·mol^{-1})	log K
27	**5d**-Co(II)	Adenine	508.2	15.71	2.706
28	**5e**	Adenine	3754	20.75	3.575
29	**5a**	Guanine	2257.6	19.46	3.354
30	**5b**	Guanine	3431.2	20.52	3.535
31	**5c**	Guanine	2962.7	20.15	3.472
32	**5d**-Zn(II)	Guanine	7461.9	22.48	3.873
33	**5d**-Cu(II)	Guanine	620.6	16.21	2.793
34	**5d**-Co(II)	Guanine	458.7	15.45	2.660
35	**5e**	Guanine	2566.8	19.79	3.409

Conditions: [complex] = 6.67 μmol·L^{-1}, pH = 7.50 (I = 0.1, NaNO$_3$), T = (303.2 ± 0.1) K.

Table 2 Binding constants (K), the Gibbs free energy change ($-\Delta G$) for mononuclear macrocyclic polyamines metal complexes **5a—5e** and nucleosides

| Entry	Host	Guest	K (L·mol^{-1})	$-\Delta G$ (kJ·mol^{-1})	log K
1	**5a**	U	9473.7	23.08	3.977
2	**5b**	U	10890.1	23.43	4.037
3	**5c**	U	9126.2	22.98	3.960
4	**5d**-Zn(II)	U	12115.9	23.70	4.083
5	**5d**-Co(II)	U	11021	23.46	4.042
6	**5e**	U	7554.1	22.51	3.878
7	**5a**	dT	5298	21.61	3.724
8	**5b**	dT	7886.5	22.62	3.987
9	**5c**	dT	3225	20.36	3.510
10	**5d**-Zn(II)	dT	7777.8	22.58	3.891
11	**5d**-Co(II)	dT	3601.8	20.64	3.357
12	**5e**	dT	5699.3	21.80	3.756
13	**5a**	G	2318.1	19.53	3.365
14	**5b**	G	2980.4	20.16	3.474
15	**5c**	G	4868.4	21.40	3.687
16	**5d**-Zn(II)	G	4388.2	21.14	3.642
17	**5d**-Co(II)	G	1835.3	18.94	3.264
18	**5e**	G	1140.5	17.74	3.057
19	**5a**	A	2604.4	19.82	3.416
20	**5b**	A	2487.5	19.71	3.396
21	**5c**	A	4032.1	20.92	3.606
22	**5d**-Zn(II)	A	2548.7	19.77	3.406
23	**5d**-Cu(II)	A	2279.2	19.49	3.358
24	**5d**-Co(II)	A	1705.8	18.76	3.232
25	**5e**	A	1931.3	19.07	3.286
26	**5a**	C	3998.6	20.90	3.602
27	**5b**	C	2195.6	19.39	3.342
28	**5c**	C	4543.4	21.23	3.657
29	**5d**-Zn(II)	C	3261.6	20.39	3.513
30	**5d**-Cu(II)	C	4051.3	20.94	3.608
31	**5d**-Co(II)	C	1555.0	18.52	3.192
32	**5e**	C	1571.0	18.55	3.196

Conditions: [complex] = 6.67 μmol·L^{-1}, pH = 7.50 (I = 0.1, NaNO$_3$), T = (303.2 ± 0.1) K.

Scheme 2 Structure of 5-hydroxymethyluracil
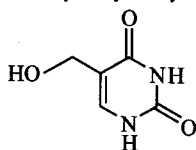
polyamine complex greatly. In the study, Zn^{2+}-cyclen (cyclen = 1, 4, 7, 10-tetraaza-cyclododecane) derivatives gave much higher affinity than Cu^{2+}-cyclen derivatives and Co^{2+}-cyclen derivatives. It implies that zinc is essential for the recognition of bases. This conclusion is in accord with that reported in the reference.[26] For instance, the Zn^{2+}-cyclen derivatives appended with aromatic pendant group such as **5c** and **5d** provide higher affinity to bases (uracil, adenine, guanine and 5-hydroxymethyluracil) than those appended with nonaromatic side chain. The reason should be that **5c—5d** interact with bases in various fashions via electrostatic, hydrogen bond and π-π stacking effect between two aromatic rings. No matter what the guest belongs to purine or pyrimidine, the guest is able to be recognized more efficiently by the Zn(II) complexes containing benzene ring in their side chain (**5d**) than containing pyridine at the same situation (**5a—5c**). We believe that the π-electron density of benzene ring higher than pyridine ring is the main reason. Consequently, the stacking effect of benzene ring is greater than pyridine ring. However, the nitrogen atom of pyridine ring in complexation reduces the combined ability of Zn^{2+} with guest. Moreover oxygen atom is also to be contained in complexation. It is similar to nitrogen atom, therefore the recognition ability of Zn^{2+} complexes turns down as the pyridine side chain containing oxygen atom.

As shown in Table 2, there are a lot of similarities between the recognition of bases and nucleosides by mononuclear macrocyclic polyamine metal complexes. These complexes are able to recognize all of the general nucleosides. As bases, the recognition of nucleosides by macrocyclic polyamine metal complexes is influenced by the species of metal ion greatly. Zinc is also the most essential element in this kind of molecular recognition. The general sequence is $5\text{-}Zn^{2+} > 5\text{-}Cu^{2+} > 5\text{-}Co^{2+}$. There is an exception for this conclusion: **5d**-Cu^{2+} recognizes cytidine better than **5d**-Zn^{2+}. The pyridine ring in the side chain of macrocyclic polyamine can interact with the aromatic ring in the substrate via stacking effect, which is of great advantage to the formation of supramolecular system (Scheme 3). Therefore, the recognition of most nucleosides by **5a** is better than **5e** with the exception of that **5e** recognizes dT better than **5a**. It looks like there are some different effects between 2'-OH and 2'-H. However, further investigation would be required in order to substantiate this possibility. As for the same kind complex, usually the recognition of base is better than the corresponding nucleoside because the size of ribose or deoxyribose of nucleoside is too large to interact with the complex and these ribose or deoxyribose will impede the formation of supramolecular

system.

Scheme 3 Simple mechanism of recognition for **1c** with uracil, U, dT, A and G
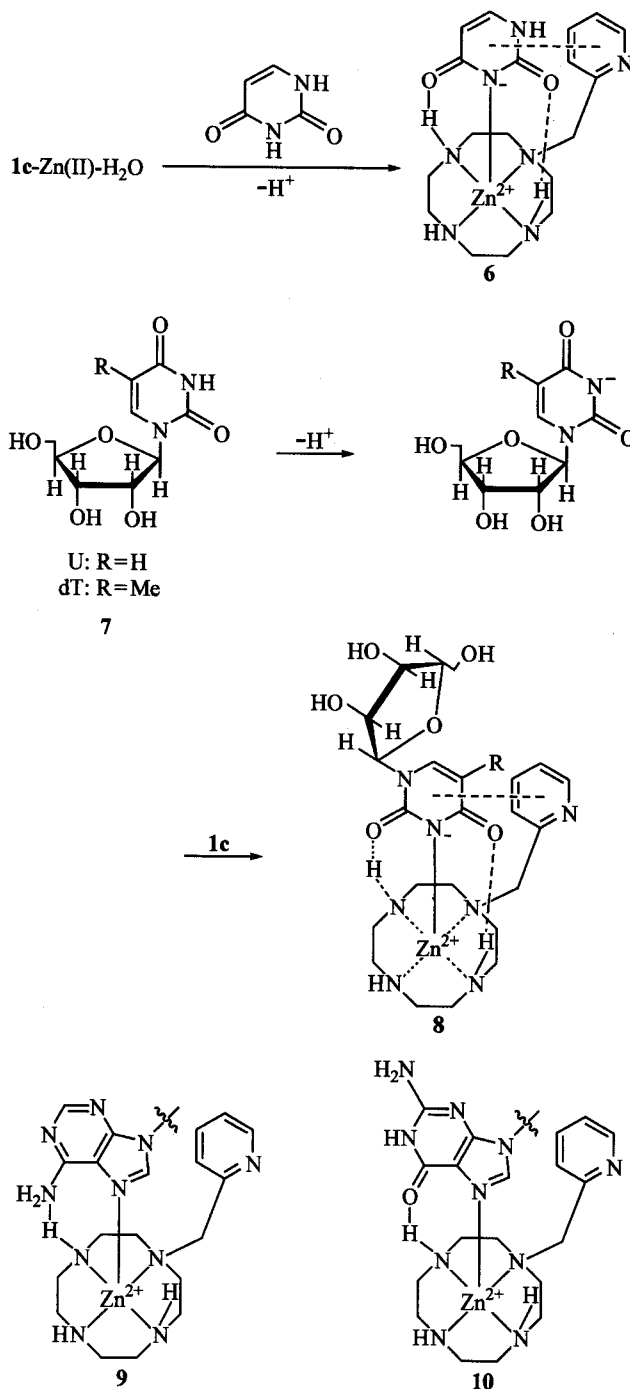
As a special substrate, uracil catches our attention because it can be recognized in the highest efficiency by mononuclear macrocyclic polyamine metal complexes. The recognition mechanism of uracil, U and dT by mononuclear macrocyclic polyamine Zn^{2+} complex **5c** is shown in Scheme 3. When **1c** interacts with the uracil and its homologues, an equivalent proton is released from the imide NH group to form stable 1 : 1 complexes Zn^{2+}-cyclen-U$^-$ (**6** and **8**). This complex had been shown to possess a

stronger affinity to those guest molecules. On the other hand, when **1c** interacts with guanine or its homologues, no proton is released from the Zn^{2+}-cyclen-A or Zn^{2+}-cyclen-G (**9** and **10**). This means that there is only one hydrogen bond between complex **1c** and Gua or G. From above-mentioned results, in our opinion, the main promotion of the molecular recognition is the formation of a bond between Zn^{2+}-imide N^- anion and guest, and two complementary hydrogen bonds between host and guest are the most important factor to affect the recognition difference for different bases and nucleoside. The steric effect of host and guest also is one of the effect factors, and this had lead to the remarkable difference of bases and the corresponding nucleoside. The pyridine ring also can recognize the aromatic ring in the substrate via π-π stacking effect.

Experimental

Reagents

All of reagents and solvents used were commercially available without further purification. UV spectra were recorded on a JASCO U-530 UV/vis spectrophotometer at 30 ℃. MS spectra data were recorded on Finnigan MAT-4510 and VG Auto spectrometer 3000 mass spectrometer, respectively. ^1H NMR spectra were recorded on Brucker-DPX-300 MHz and chemical shifts are reported relative to internal Me_4Si. Elemental analyses were performed by using a Carlo-Elba 1106 elemental analytical instrument. Melting points were determined by using a micro-melting point apparatus without any corrections. CH_3CN was purified according to the standard method. Bases (uracil, cytosine, adenine, guanine) and nucleosides (U, C, A, G, dT) were purchased from Sigma and Acros. All aqueous solutions were prepared using deionized and redistilled water. The buffer solution of UV titration was Tris-base (pK_a = 10.0, at 20 ℃). The ionic strength of solution was adjusted to 0.1 with $NaNO_3$ ($NaNO_3$ was recystalized with deionized water). Halide **2** was synthesized as previously described.[27] 1,4,7-tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraaza cyclododecane was prepared according to literature.[28]

Synthesis of macrocyclic polyamine metal complexes **5a—5e**

General procedure of the syntheses of 5a—5e   Under N_2 atmosphere, a solution of acetonitrile (50 mL), alkyl halide or **2** (2.10 mmol) and 1,4,7-tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (1.0 g, 2.10 mmol) was refluxed in the presence of anhydrous potassium carbonate (3.45 g, 2.50 mmol) for 72 h. After removal of inorganic salts, the solvent was evaporated and the resulting residue was dissolved in 50 mL of chloroform. And then triethylamine (0.42 mL, 4.2 mmol) and benzyl chloroformate (0.7 g, 4.2 mmol) were added at 0 ℃. After being stirred overnight at room temperature, the reaction mixture was concentrated *in vacuo*. The resulting

crude product was purified by silica gel chromatography to afford **3**.

1-[6-(*n-Dodecoxymethyl*)-pyridine-2-yl-methyl]-4, 7,10-*tris*(*tert-butyloxy carbonyl*)-1,4,7,10-*tetraazacyclododecane* (3a)   Pale yellow amorphous solid (yield 82.7%). Eluent: EtOAc:petroleum ether = 1:1 (*V:V*). ^1H NMR (CDCl$_3$, 300 MHz) δ: 0.99 (t, *J* = 6.60 Hz, 3H, CH$_3$), 1.40 [s, 18H, CH$_2$(CH$_2$)$_9$CH$_3$], 1.58 [s, 27H, OC(CH$_3$)$_3$], 1.70—1.76 [m, 4H, OCH$_2$CH$_2$-(CH$_2$)$_9$], 2.74—2.82 (m, 4H, CH$_2$NCH$_2$), 3.48 (t, 8H, *J* = 6.60 Hz, CH$_2$NCH$_2$), 3.71—3.74 (m, 4H, CH$_2$NCH$_2$), 3.81 (s, 2H, OCH$_2$Py), 4.59 (s, 2H, NCH$_2$Py), 7.42 (d, *J* = 7.40 Hz, 3H, PyH); MS *m/z* (%): 649 (M$^+$ − C$_8$H$_{17}$ + 1, 5). Anal. calcd for C$_{42}$H$_{75}$N$_5$O$_7$: C 66.19, H 9.92, N 9.19; found C 66.21, H 9.90, N 9.23.

1-[6-(*Methoxymethyl*)-pyridine-2-yl-methyl]-4,7, 10-*tris*(*tert-butyloxycarbonyl*)-1,4,7,10-*tetraazacyclododecane* (3b)   Pale yellow amorphous solid (yield 89.0%). Eluent: EtOAc:petroleum ether = 1.5:1 (*V:V*). ^1H NMR (CDCl$_3$, 300 MHz) δ: 1.44 [s, 27H, OC-(CH$_3$)$_3$], 3.29—3.63 (m, 16H, CH$_2$NCH$_2$; s, 3H, OCH$_3$), 3.79 (s, 2H, OCH$_2$Py), 4.53 (s, 2H, NCH$_2$Py), 7.28 (d, *J* = 7.70 Hz, 1H, PyH$_4$), 7.63 (d, *J* = 7.70 Hz, 2H, PyH$_3$, PyH$_5$); MS *m/z* (%): 608 (M$^+$ + 1, 15). Anal. calcd for C$_{31}$H$_{53}$N$_5$O$_7$: C 61.26, H 8.79, N 11.52; found C 61.30, H 8.82, N 11.47.

1-(2-*Pyridine-methyl*)-4,7,10-*tris*(*tert-butyloxycarbonyl*)-1,4,7,10-*tetraazacyclo dodecane* (3c)   Colorless amorphous solid (yield 55.8%). Eluent: EtOAc: petroleum ether = 1.5:1 (*V:V*). ^1H NMR (CDCl$_3$, 300 MHz) δ: 1.37 [s, 27H, OC(CH$_3$)$_3$], 2.86 (t, *J* = 6.70 Hz, 4H, CH$_2$NCH$_2$), 3.42—3.90 (brs, 2H, CONCH$_2$), 3.96 (s, 2H, CH$_2$Py), 7.27 (d, *J* = 7.60 Hz, 1H, PyH$_4$), 7.40 (d, *J* = 7.60 Hz, 1H, PyH$_5$), 7.73 (d, *J* = 7.60 Hz, 1H, PyH$_3$), 8.67 (d, *J* = 7.60 Hz, 1H, PyH$_6$); MS *m/z* (%): 564 (M$^+$ + 1, 100). Anal. calcd for C$_{29}$H$_{49}$N$_5$O$_6$: C 61.79, H 8.76, N 12.42; found C 61.74, H 8.73, N 12.52.

1-*Benzyl*-4,7,10-*tris*(*tert-butyloxycarbonyl*)-1,4,7, 10-*tetraazacyclo dodecane* (3d)   Colorless amorphous solid (yield 94.7%). Eluent: EtOAc:petroleum ether = 1:2 (*V:V*). ^1H NMR (CDCl$_3$, 300 MHz) δ: 1.50 [s, 27H, OC(CH$_3$)$_3$], 2.44—2.80 (brs, 4H, NCH$_2$), 3.36—3.51 (brs, 8H, CONCH$_2$), 3.70 (brs, 4H, CONCH$_2$), 3.84 (s, 2H, PhCH$_2$), 7.38 (d, *J* = 7.10 Hz, 5H, ArH); MS *m/z* (%): 562 (M$^+$ + 1, 4). Anal. calcd for C$_{30}$H$_{50}$N$_4$O$_6$: C 64.03, H 8.96, N 9.96; found C 64.09, H 9.00, N 9.93.

1-*n-Dodecyl*-4,7,10-*tris*(*tert-butyloxycarbonyl*)-1, 4,7,10-*tetraazacyclododecane* (3e)   Pale yellow amorphous solid (yield 22.0%). Eluent: EtOAc:petroleum ether = 1:3 (*V:V*). ^1H NMR (CDCl$_3$, 300 MHz) δ: 0.88 (t, *J* = 6.60 Hz, 3H, CH$_3$), 1.22—1.31 [m, 18H, CH$_2$(CH$_2$)$_9$CH$_3$], 1.40 [s, 27H, OC(CH$_3$)$_3$],

1.64—1.66 [m, 2H, CH$_2$(CH$_2$)$_9$CH$_3$], 2.47 [t, J = 6.00 Hz, 2H, CH$_2$(CH$_2$)$_{10}$CH$_3$], 3.28—3.37 (m, 16H, CH$_2$NCH$_2$); MS m/z (%): 542 (M$^+$ + 1 – C$_7$H$_{15}$, 5), 485 (M$^+$ – C$_{11}$H$_{23}$, 90). Anal. calcd for C$_{35}$H$_{68}$N$_4$O$_6$: C 65.59, H 10.69, N 8.74; found C 65.48, H 10.71, N 8.70.

1-[6-(n-Dodecoxymethyl)-pyridine-2-yl-methyl]-1, 4, 7, 10-tetraaza cyclododecane quadrihydrobromide salt (4a)　　To a solution of 3Boc-cyclen 3a (0.48 g, 0.63 mmol) and ethanol (5 mL) at 0 ℃, aqueous hydrobromic acid (40%, 5 mL) was added slowly. Stirred overnight at room temperature, and then the reaction mixture was concentrated in vacuo below 40 ℃. The resulting crude powder was crystallized from EtOH/HBr (24%) to afford 4a as white crystals (yield 81.5%). m.p. 210 ℃ (dec.); ^{1}H NMR (D$_2$O, 300 MHz) δ: 0.70 (t, J = 6.50 Hz, 3H, CH$_3$), 1.34 [s, 18H, CH$_2$(CH$_2$)$_9$CH$_3$], 1.82—1.88 [m, 4H, OCH$_2$CH$_2$(CH$_2$)$_9$CH$_3$, m, 8H, CH$_2$CH$_2$-NH], 2.91—2.98 (m, 4H, NCH$_2$PyCH$_2$O; m, 8H, NHCH$_2$), 7.74 (d, J = 7.60 Hz, 3H, PyH); FAB-MS m/z (%): 462 (M$^+$ + 1 – 4HBr, 100). Anal. calcd for C$_{27}$H$_{55}$N$_5$OBr$_4$: C 59.43, H 10.16, N 12.83; found C 59.38, H 10.13, N 12.88.

1-[6-(Methoxymethyl)-pyridine-2-yl-methyl]-1, 4, 7, 10-tetraazacyclododecane quadrihydrobromide salt (4b)

The synthetic method of 4b is similar to 4a. White crystals (yield 90.3%). m.p. 204 ℃ (dec.); ^{1}H NMR (D$_2$O, 300 MHz) δ: 3.10—3.21 (m, 16H, CH$_2$N-CH$_2$), 3.56 (s, 2H, CH$_3$OCH$_2$Py; s, 3H, OCH$_3$), 4.13 (s, 2H, NCH$_2$Py), 7.86 (d, J = 7.90 Hz, 2H, PyH$_3$, PyH$_5$); FAB-MS m/z (%): 308 (M$^+$ + 1 – 4HBr, 20). Anal. calcd for C$_{16}$H$_{33}$N$_5$OBr$_4$: C 30.61, H 5.30, N 11.17; found C 30.56, H 5.40, N 10.98.

1-(2-Pyridine-methyl)-1, 4, 7, 10-tetraazacyclodo-decane quadrihydrobromide salt (4c)　　The synthetic method of 4c is similar to 4a. White crystals (yield 73.1%). m.p. 218 ℃ (dec.); ^{1}H NMR (D$_2$O, 300 MHz, relative to internal (CD$_3$)$_3$SiCD$_2$CD$_2$SO$_3$Na) δ: 2.80—3.08 (m, 8H, NHCH$_2$), 3.15 (t, J = 3.64 Hz, 4H, CH$_2$NCH$_2$), 3.38 (t, J = 3.51 Hz, 4H, NHCH$_2$CH$_2$), 4.09 (s, 2H, CH$_2$Py), 7.87 (d, J = 7.90 Hz, 2H, PyH$_4$, PyH$_5$), 8.37 (d, J = 7.90 Hz, 1H, PyH$_3$), 8.67 (d, J = 7.90 Hz, 1H, PyH$_6$); FAB-MS m/z (%): 264 (M$^+$ + 1 – 4HBr, 10). Anal. calcd for C$_{14}$H$_{29}$N$_5$OBr$_4$: C 28.64, H 4.98, N 11.93; found C 28.60, H 5.09, N 11.91.

1-Benzyl-1, 4, 7, 10-tetraazacyclododecane trihydrobromide salt (4d)　　The synthetic method of 4d is similar to 4a. White crystals (yield 93.9%). m.p. 238 ℃ (dec.); ^{1}H NMR (D$_2$O, 300 MHz) δ: 2.90—3.11 (m, 12H, CH$_2$NHCH$_2$), 3.14—3.17 (m, 4H, CH$_2$N), 3.85 (s, 2H, CH$_2$Ph), 7.46 (d, J = 7.60 Hz, 5H, ArH); FAB-MS m/z (%): 263 (M$^+$ + 1 – 3HBr, 10). Anal. calcd for C$_{15}$H$_{29}$N$_4$Br$_3$: C 35.67, H 5.79, N 11.09; found C 35.60, H 5.83, N 11.08.

1-n-Dodecyl-1, 4, 7, 10-tetraazacyclododecane trihy-

drobromide salt (4e)　　The synthetic method of 4d is similar to 4a. White crystals (yield 94.4%); m.p. 228 ℃ (dec.); ^{1}H NMR (D$_2$O, 300 MHz): 0.81 (t, J = 6.20 Hz, 3H, CH$_3$), 1.24—1.57 [m, 18H, (CH$_2$)$_9$CH$_3$], 1.70—1.72 [m, 2H, CH$_2$(CH$_2$)$_{10}$CH$_3$], 2.90[t, J = 6.10 Hz, 2H, CH$_2$(CH$_2$)$_{10}$CH$_3$], 3.07 (s, 16H, CH$_2$NCH$_2$); FAB-MS m/z (%): 341 (M$^+$ + 1 – 3HBr, 5). Anal. calcd for C$_{20}$H$_{47}$N$_4$Br$_3$: C 41.18, H 8.12, N 9.60; found C 41.21, H 8.15, N 9.61.

1-[6-(n-Dodecoxymethyl)-pyridine-2-yl-methyl]-1, 4, 7, 10-tetraazacyclodode-cane Zn(II) complex [5a·(ClO$_4$)$_2$·H$_2$O]　　The salt of 4a quadrihydrobromide (0.3 g, 0.46 mmol) was dissolved in water (10 mL), and the pH of the solution was adjusted to 12 with aqueous NaOH. The alkaline solution was extracted with CH$_2$Cl$_2$ (30 mL × 5), then the solvent was evaporated. An solution of EtOH (10 mL), the obtained acid-free ligand and Zn(ClO$_4$)$_2$·6H$_2$O (0.14 g, 0.38 mmol) was stirred at 60 ℃ for 2 h. After being cooled, the solids were filtered off, washed with cool EtOH, the residue was crystallized from H$_2$O/EtOH to obtained colorless crystals (yield 34.4%). m.p. 218—219 ℃ (dec.); ^{1}H NMR (D$_2$O, 300 MHz) δ: 0.88 (t, J = 6.40 Hz, 3H, CH$_3$), 1.28 [s, 18H, (CH$_2$)$_9$CH$_3$], 2.76—2.91 [m, 16H, CH$_2$NCH$_2$; m, 4H, NCH$_2$PyCH$_2$O; m, 4H, OCH$_2$CH$_2$(CH$_2$)$_9$CH$_3$], 7.35 (d, J = 7.50 Hz, 3H, PyH); FAB-MS m/z (%): 525 (M$^+$ + 1 – 2ClO$_4$ – H$_2$O, 15). Anal. calcd for ZnC$_{27}$H$_{53}$N$_5$O$_{10}$Cl$_2$: C 43.59, H 7.18, N 9.41; found C 43.54, H 7.21, N 9.43.

1-[6-(Methoxymethyl)-pyridine-2-yl-methyl]-1, 4, 7, 10-tetraazacyclododecane Zn(II) complex [5b·(ClO$_4$)$_2$·H$_2$O]　　The synthetic method of 5b is similar to above. Colorless crystals (yield 88.2%). m.p. 240—241 ℃ (dec.); ^{1}H NMR (D$_2$O, 300 MHz) δ: 2.75—3.17 (m, 16H, CH$_2$NCH$_2$), 3.40 (s, 2H, OCH$_3$), 3.54 (s, 2H, CH$_3$OCH$_2$Py), 4.23 (s, 2H, PyCH$_2$N), 7.41 (d, J = 7.80 Hz, 2H, PyH$_3$, PyH$_5$), 8.01 (d, J = 7.80 Hz, 1H, PyH$_4$); FAB-MS m/z (%): 373 (M$^+$ – 2ClO$_4$ – H$_2$O, 38), 341 (M$^+$ – 1 – 2ClO$_4$ – H$_2$O – OCH$_3$, 15), 327 (M$^+$ – 1 – 2ClO$_4$ – 2H$_2$O – CH$_2$OCH$_3$, 10). Anal. calcd for ZnC$_{16}$H$_{31}$N$_5$O$_{10}$Cl$_2$: C 32.19, H 5.30, N 11.88; found C 32.62, H 5.32, N 11.84.

1-(2-Pyridine-methyl)-1, 4, 7, 10-tetraazacyclodo-decane Zn(II) complex [5c·(ClO$_4$)$_2$·H$_2$O]　　Colorless crystals (yield 71.4%). m.p. 177—178 ℃ (dec.); ^{1}H NMR (D$_2$O, 300 MHz) δ: 2.74—3.28 (m, 16H, CH$_2$NCH$_2$), 4.25 (s, 2H, PyCH$_2$), 7.62 (d, J = 7.70 Hz, 2H, PyH$_4$, PyH$_5$), 8.08 (d, J = 7.70 Hz, 1H, PyH$_6$), 8.67 (d, J = 7.70 Hz, 1H, PyH$_3$); FAB-MS m/z (%): 373 (M$^+$ – 1 – 2ClO$_4$ – H$_2$O, 50). Anal. calcd for ZnC$_{14}$H$_{27}$N$_5$O$_9$Cl$_2$: C 30.82, H 4.99, N 12.83; found C 30.88, H 5.03, N 12.78.

1-Benzyl-1, 4, 7, 10-tetraazacyclododecane Zn(II) complex [5d·(ClO$_4$)$_2$·H$_2$O]　　White solid (yield 32.4%). m.p. 254—255 ℃ (dec.); ^{1}H NMR (D$_2$O, 300 MHz) δ: 2.78—2.89 (m, 8H, CH$_2$NHCH$_2$),

2.97—3.04 (m, 4H, NH CH$_2$), 3.21 (s, 2H, PhCH$_2$), 4.01—4.09 (m, 4H, CH$_2$NHCH$_2$Py), 7.49 (d, J = 7.60 Hz, 5H, ArH); FAB-MS m/z (%): 327 (M$^+$ +1 − 2ClO$_4$ − H$_2$O, 15). Anal. calcd for ZnC$_{15}$H$_{28}$N$_4$O$_9$Cl$_2$: C 33.08, H 5.18, N 10.29; found C 33.03, H 5.21, N 10.27.

1-*Benzyl*-1, 4, 7, 10-*tetraazacyclododecane* Cu (II) complex [**5d** · (ClO$_4$)$_2$ · H$_2$O]   Blue crystals (yield 92.%). m.p. 90—91 ℃ (easy sop); ^{1}H NMR (D$_2$O, 300 MHz) δ: 2.77—2.85 (m, 4H, CH$_2$NHCH$_2$), 3.30—3.35 (m, 4H, ArNCH$_2$), 3.51—3.58 (m, 8H, CH$_2$N), 3.84 (s, 2H, ArCH$_2$), 7.46 (d, J = 7.50 Hz, 5H, ArH); FAB-MS m/z (%): 325 (M$^+$ + 2ClO$_4$ − H$_2$O, 5). Anal. calcd for CuC$_{15}$H$_{28}$N$_4$O$_9$Cl$_2$: C 33.19, H 5.20, N 10.32; found C 33.21, H 5.23, N 10.28.

1-*Benzyl*-1, 4, 7, 10-*tetraazacyclododecane* Co (II) complex [**5d**·(ClO$_4$)$_2$·H$_2$O]   Red solid (yield 73%). m.p. 138 ℃ (easy sop); ^{1}H NMR (D$_2$O, 300 MHz) δ: 2.29—3.40 (m, 16H, CH$_2$NHCH$_2$), 3.72 (s, 2H, CH$_2$Py), 7.48 (d, J = 7.40 Hz, 5H, ArH); FAB-MS m/z (%): 323 (M$^+$ +1 − 2ClO$_4$ − H$_2$O, 10), 242 (M$^+$ − 1 − 2ClO$_4$ − H$_2$O − Ph, 13). Anal. calcd for CoC$_{15}$H$_{28}$N$_4$O$_9$Cl$_2$: C 33.47, H 5.24, N 10.41; found C 33.50, H 5.26, N 10.45.

1-*n*-*Dodecyl*-1,4,7,10-*tetraazacyclododecane* Zn(II) complex [**5e** · (ClO$_4$)$_2$ · H$_2$O]   White solid (yield 70.4%). m.p. 84—85 ℃ (dec.); ^{1}H NMR (D$_2$O, 300 MHz) δ: 0.85 (t, J = 6.50 Hz, 3H, CH$_3$), 1.35—1.51 [m, 18H, (CH$_2$)$_9$CH$_3$], 1.70—1.76 [m, 2H, CH$_2$(CH$_2$)$_{10}$CH$_3$], 2.94 [t, J = 6.20 Hz, 2H, NCH$_2$-(CH$_2$)$_{10}$CH$_3$], 3.03—3.19 (m, 16H, CH$_2$NHCH$_2$); FAB-MS m/z (%): 407 (M$^+$ − 1 − 2ClO$_4$ − H$_2$O, 8). Anal. calcd for ZnC$_{20}$H$_{46}$N$_4$O$_9$Cl$_2$: C 38.57, H 7.44, N 8.99; found C 38.53, H 7.49, N 9.02.

UV *Titration*

UV spectra were recorded on a JASCO U-530 UV/vis spectrophotometer at (30 ± 0.1) ℃. The 3.0 mL of solution of bases and nucleosides ([Guest] = 1.67—10.00 μmol·L^{-1}) in 41 mmol·L^{-1} Tris buffer [pH = 7.50 with I = 0.1 (NaNO$_3$)] was put into a quartz cell. After the cell temperature has become constant at 30 ℃ with a thermostatic cell compartment, the solution of a metal complex (concentration was 6.67 μmol·L^{-1}) in 41 mmol·L^{-1} Tris buffer was portion-wise added. Different absorption spectra were obtained directly using the instrument according to its normal procedures. The titration was repeated three times.

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