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Recognition of Thymine and Related Nucleosides by a Zn^{II}-Cyclen Complex Bearing a Ferrocenyl Pendant

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A cyclen derivative bearing a ferrocenyl arm (**L**) and a series of its Zn^{II} complexes [Zn**L**(OH_2)][ClO_4]$_2$ (**C1**), [Zn**L**(OH)]-[ClO_4] (**C2**), and [Zn**L**(Cl)][ClO_4]·CH_3CN (**C3**) (cyclen = 1,4,7,10-tetraazacyclododecane, **L** = 1-(ferrocenemethyl)-1,4,7,10-tetraazacyclododecane) have been prepared and characterized spectroscopically. An X-ray structure determination confirmed the formation of complex **C1** and revealed that the coordinated water participates in hydrogen bonding with the perchlorate counter ions. The pK_a value for deprotonation of the water molecule determined by potentiometric titration was found to be 7.36 ± 0.09 at 25 °C and $I = 0.1$ (KNO_3). The possibility of using complex **C1** as a potential sensor for thymine derivatives in aqueous solution has been examined. Shifts in the ^1H and ^{13}C NMR resonances showed the binding occurred with thymine (T) and two thymine derivatives, thymidine (dT) and thymidine 5′-monophosphate (TMP^{2-}). Significant shifts of the $\nu_{C=O}$ and $\nu_{C=C}$ vibrations of the thymine derivatives were also observed via IR spectroscopy upon complexation with the receptor. The thymine adduct, [Zn**L**(thymine anion)][ClO_4]•$2H_2O$ (**C4**), has been crystallized and characterized. The X-ray structure of **C4** confirmed the thymine binding to the receptor, and the short Zn–N(thymine) distance of 1.975(5) Å indicated clearly that the ferrocenyl arm does not affect the complexation of the DNA base. In contrast to the large spectral changes, electrochemical studies showed a small shift of the reversible potential of the redox couple Fc^+/Fc (Fc = ferrocene) and subtle changes in voltammetry upon the addition of an excess of dT, TMP^{2-}, and guanine (dG) at physiological pH, indicating the level of interaction is similar in both Fc and Fc^+ forms.

Introduction

The development of artificial receptors for DNA/RNA bases continues to attract the attention of scientists because of their potential for use as nucleotide sensors or for the determination of low concentrations of therapeutic agents.[1] Many of these receptors are organic molecules, with a molecular structure designed to mimic naturally occurring noncovalent bonds, such as hydrogen bonding, hydrophobic, or electrostatic interactions, etc. However, when polymeric assemblies are used, these interactions are sufficiently strong in aqueous solution to allow the binding and detection of particular analytes. As it is known that metal coordination is normally much stronger than the noncovalent interactions, there have been reports describing synthesized nucleobase receptors containing metal ions. For example, Kimura et al. originally discovered that thymidine nucleoside (dT) and its homologues selectively bind to Zn^{2+}-cyclen (cyclen = 1,4,7,-10-tetraazacyclododecane) in aqueous solution at physiological pH.[2,3] The products are 1:1 adducts in which the nucleobase is deprotonated and binds to Zn^{II} via the deprotonated imide. Recently, Chin et al. reported a new Cd^{2+} complex able to act as a receptor for cytidine in DMSO.[1] Sadler et al. developed a Ru^{2+} complex which binds guanine (dG), inosine (Ino), and thymidine (dT).[4]

Another challenge in this area of research has been to develop a sensitive and practical analytical method that can be used to monitor the binding of these artificial receptors to the targeted nucleobase. To achieve this, the insertion of an acridine-pendant to the Zn^{2+}-cyclen receptor was carried out by Kimura et al., and detection was achieved via fluorescence studies.[5] A strong decay in the fluorescence

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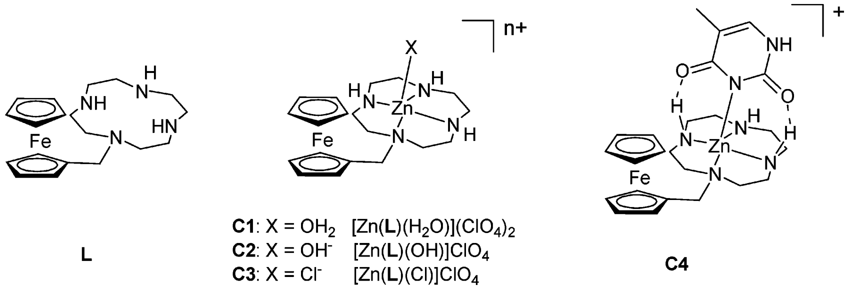

Figure 1. Representations of the structures of **L** and **C1**−**C4**.

intensity was observed only in the presence of thymidine (dT) or inosine (Ino) at pH 7.6. The attachment of the redox-active anthraquinone moiety to the receptor allowed nucleobase binding to be detected via electrochemical methods[6] because a shift in the reversible potential of the redox response occurs in aqueous solution upon the addition of excess amounts of dT. This shift in potential is caused by an increase in electrostatic repulsion between the dihydroanthraquinone arm and dT which causes a weakening of $\pi\cdots\pi$ interactions in the oxidized form of the receptor upon reduction of the antraquinone moiety.

Many redox-active supramolecular receptors are available for electrochemical sensor development. However, the ferrocene group has been the most commonly used because of its stable, reversible electrochemistry,[7] and we have previously reported the electrochemical response of a ferrocenyl bearing Zn^{2+}-cyclen receptor upon the addition of a DNA base.[8] The receptor used, the Zn^{2+} complex of 1-(ferrocenemethyl)-1,4,7,10-tetraazacyclododecane (**L**) (Figure 1), showed a shift of −10 mV upon the addition of an excess of thymine (T) in acetonitrile. However, from the point of view of practical applications, it is desirable for biosensors to operate in water, rather than organic solvents. Furthermore, to enhance the sensitivity of electrochemical response, it would also be desirable if the binding of the oxidized form of the receptor is significantly different to that found in the reduced form. In contrast to the anthraquinone system,[6] the oxidized form of our receptor contains a ferricinium moiety and therefore has a positive charge. This change from neutral to positive that occurs on oxidation could significantly affect the binding of the nucleobase to the complex, especially when the negatively charged thyminidine 5′-monophosphate (TMP^{2-}) is the sensing target.

In this paper, we present the redox behavior of a ferrocenyl receptor couple in aqueous solution upon addition of an excess amount of dT and TMP^{2-} and the noncomplementary DNA base dG to our receptor. In addition, the synthesis and analytical and X-ray structural characterizations of three complexes formed by **L** are described ([Zn**L**(OH$_2$)][ClO$_4$]$_2$ (**C1**), [Zn**L**(Cl)][ClO$_4$]·CH$_3$CN (**C3**), and the thymine adduct [Zn**L**(thymine anion)][ClO$_4$]·2H$_2$O (**C4**)) (see Figure 1).

Experimental Section

Materials. All chemicals were of reagent grade quality or better and were used as supplied by the manufacturer. Solvents were used as received or dried over 4 Å molecular sieves or dried following literature procedures.[9] High-purity nitrogen gas was used to deoxygenate solutions used in pH titrations and electrochemical experiments. Deionized water used to prepare solutions was boiled for 2 h under a flux of nitrogen prior to use.

Spectroscopic Instrumentation. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 30 °C in deuterated solvents using either Bruker AC200, Bruker DPX300, or Avance DRX400 Bruker spectrometers. The residual solvent resonances were used as the internal reference for nonaqueous solvents, sodium (2,2,3,3-d_4-3-(trimethylsilyl))propionate (TMSP-D) for NMR studies in D$_2$O and phosphoric acid for ^{31}P NMR. The abbreviations for the peak multiplicities are as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). 2D NMR experiments were conducted on some complexes, and the data were analyzed with XWinNMR software. Infrared spectra were recorded using KBr disks with Bruker IFS 55 FTIR spectrophotometer at a resolution of 4 cm^{-1}. CHN analyses were performed by the Campbell Microanalytical Service, University of Otago, Dunedin, NZ.

Potentiometric pH Titrations. The solution pH was measured with a Metrohm electrode, fitted to a Metrohm pH meter. A Metrohm 808 Titrando (5 mL burette) was used to dispense the small volumes of KOH solution required in titration experiments. All pH measurements were made at 25.0 ± 0.1 °C (temperature maintained by a Thermoline Scientific Unistat water bath) and at a ionic strength of $I = 0.10$ (KNO$_3$). The pH electrode was calibrated using standard phthalate and phosphate buffer solutions. Solutions for pH titrations were prepared using CO$_2$-free water (boiled for 2 h under a flux of nitrogen), and each titration was performed in duplicate in a sealed vessel under a nitrogen atmosphere. KOH solutions (0.1 M) were standardized against dried potassium hydrogen phthalate.

Electrochemical Studies. Cyclic voltammograms were performed using a BAS Epsilon potentiostat operated by BASi Epsilon-EC Software, version 1.50.69_XP. A typical three electrode cell was employed comprising a glassy carbon working electrode, an Ag/AgCl/(3 M KCl$_{aq}$) reference electrode, and a Pt counter electrode. All measurements were recorded at 20 (±2) °C (inside a Faraday cage) and under a N$_2$ atmosphere. The solution was purged with N$_2$ for at least 5 min prior to measurements. Scan rates over the range of 10−1000 mV s^{-1} were employed. The voltam-

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metry for the known reversible one-electron oxidation of ferrocene in CH_3CN (0.5 M in $[But_4N][PF_6]$) was used to calculate the area of the glassy carbon working electrode (0.07 cm^2) using the Randles−Sevcik equation and the diffusion coefficient of ferrocene 1.70×10^{-5} cm^2 s^{-1}.[10,11] The potentials measured versus Ag/AgCl/(3 M KCl_{aq}) were converted to the normal hydrogen electrode (NHE) scale by addition of +210 mV (uncorrected for temperature differences).[12] Solutions for studies of the binding of **C1** with DNA nucleosides contained 75 mM buffer and 1 mM of **C1** and the ionic strength was adjusted to 0.2 M with $NaClO_4$, taking into account the contribution from all other charged species present. The MOPS (3-(*N*-morpholino)propanesulfonic acid) buffer was prepared using methods described at http://www.liv.ac.uk/buffers/buffercalc.html. The error in pH values reported is estimated to be ±0.05. All solutions were filtered with a 0.22 μm membrane filter prior to measurements.

Caution: *Although no problems were encountered in this work, metal perchlorate complexes are potentially explosive. They should be prepared in small quantities and handled with care.*

1-(Ferrocenemethyl)-1,4,7,10-tetraazacyclododecane (L). L was synthesized following the general procedure published by Sisti et al.[13]

$[Zn(L)(H_2O)](ClO_4)_2$ (C1). L (80 mg, 0.22 mmol) and $Zn(ClO_4)_2 \cdot 6H_2O$ (80 mg, 0.22 mmol) were dissolved in a 1:1 mixture of water (15 mL) and acetonitrile (15 mL). The pH was adjusted to 5.0 with dilute $HClO_4$ (0.1 M), and the solution was heated to 80 °C for 30 min. The solvent was then removed in vacuo; the yellow-orange solid washed several times with small portions of ethanol and diethyl ether, filtered, and air-dried. Yellow-orange crystals suitable for X-ray crystallography were obtained by recrystallization from water. Yield: 100 mg (72%). Anal. Found (%): C, 34.4; H, 4.9; N, 8.2. Calcd for $ZnFeC_{19}H_{32}N_4O_9Cl_2$ (%): C, 34.9; H, 4.9; N, 8.5. Major IR bands (KBr, ν, cm^{-1}): 3521 m br, 3286 m, 3257 m, 3092 w, 2934 m, 2885 m, 1466 m, 1442 w, 1383 w, 1298 w, 1285 w, 1231 w, 1090 s b, 995 m, 978 m, 946 w, 924 w, 837 w, 812 w, 623 m. ^1H NMR (DMSO-d_6): δ 2.46−2.55 (m, 6H, C*H*$_2$ cyclen), 2.60−2.80 (m, 11H, C*H*$_2$ cyclen, N*H* cyclen), 2.83−2.93 (m, 2H, C*H*$_2$ cyclen), 3.70 (s, 2H, Cp-C*H*$_2$-cyclen), 4.17 (s, 5H, C*H* Cp), 4.23 (m, 2H, C*H* Cp), 4.27 br, 1H, N*H*), 4.32 (m, 2H, C*H* Cp), 4.35 (br, 2H, N*H*). ^{13}C NMR (DMSO-d_6): δ 42.01 (*C*H$_2$ cyclen), 43.53 (*C*H$_2$ cyclen), 44.30 (*C*H$_2$ cyclen), 48.85 (*C*H$_2$ cyclen), 52.32 (Cp-*C*H$_2$-cyclen), 68.42 (*C*H Cp), 68.55 (*C*H Cp), 70.62 (*C*H Cp), 77.38 (*C* Cp).

$[Zn(L)(OH)]ClO_4$ (C2). L (50 mg, 0.14 mmol) and $Zn(ClO_4)_2 \cdot 6H_2O$ (50 mg, 0.14 mmol) were dissolved in a 1:1 mixture of water (15 mL) and acetonitrile (15 mL). The pH was adjusted to 10.0 with aqueous 0.1 M NaOH, and the solution was heated to 80 °C for 30 min. The solvent was then removed in vacuo. The yellow-orange solid was then dissolved in ethanol (20 mL), and diethyl ether was added to precipitate the complex. The yellow-orange solid was filtered and air-dried. Yield: 55 mg (74%). Anal. Found (%): C, 39.7; H, 5.6; N, 9.7. Calcd for $ZnFeC_{19}H_{31}N_4O_5Cl \cdot H_2O$ (%): C, 40.0; H, 5.8; N, 9.8. Major IR bands (KBr, ν, cm^{-1}): 3429 m br, 3300 m, 2928 w, 2881 w, 1646 w, 1442 m, 1380 m, 1282 w, 1234 w, 1089 s br, 998 w, 847 w, 671 m. ^1H NMR (DMSO-d_6): δ 2.46−2.93 (m, 16H, C*H*$_2$ cyclen ring), 3.71 (m, 3H, Cp ring-C*H*$_2$-cyclen ring and N*H*), 3.95 (br, 2H, N*H*), 4.15 (s, 5H, C*H* Cp ring), 4.23 (m, 2H, C*H* Cp ring), 4.30 (m, 2H, C*H* Cp ring). ^{13}C NMR (DMSO-d_6): δ 42.06 (*C*H$_2$ cyclen ring), 43.56 (*C*H$_2$ cyclen ring), 44.40 (*C*H$_2$ cyclen ring), 48.98 (*C*H$_2$ cyclen ring), 51.77 (Cp ring-*C*H$_2$-cyclen ring), 68.44 (*C*H Cp ring), 68.46 (*C*H Cp ring), 70.59 (*C*H Cp ring), 77.71 (*C* Cp ring).

$[Zn(L)(Cl)]ClO_4$. CH_3CN (C3). L (80 mg, 0.22 mmol) and $Zn(ClO_4)_2 \cdot 6H_2O$ (80 mg, 0.22 mmol) were dissolved in a 1:1 mixture of water (15 mL) and acetonitrile (15 mL). The pH was adjusted to 10.0 with aqueous 0.1 M NaOH, and the solution was heated to 80 °C for 30 min. The solvent was removed under vacuum, and the residual solid was then purified on a Sephadex SPC25 cation-exchange column (Na^+ form). The eluents used were aqueous 0.4M $NaClO_4$, followed by a 1:1 mixture of aqueous 1 M $NaClO_4$ and acetonitrile. The desired fractions were cautiously evaporated to dryness in vacuo, and the residual solid was extracted many times with small portions of acetone to remove as much of the $NaClO_4$ as possible. This procedure gave a yellow-orange solid. Yellow-orange crystals suitable for X-ray crystallography were obtained by diffusion of diethyl ether into a solution of **C3** in a 1:1 mixture of acetonitrile/ethanol. Yield: 15 mg (12%). Anal. Found (%): C, 38.6; H, 5.4; N, 9.6. Calcd for $ZnFeC_{19}H_{30}N_4O_4Cl_2 \cdot H_2O$ (%): C, 38.8; H, 5.5; N, 9.5. Major IR bands (KBr, ν, cm^{-1}): 3423 m br, 3296 m, 2926 w, 2879 w, 1632 m, 1458 m, 1381 m, 1298 w, 1235 w, 1091 s br, 996 w, 846 w, 746 w, 626 m. ^1H NMR (DMSO-d_6): δ 2.46−2.93 (m, 16H, C*H*$_2$ cyclen ring), 3.69 (s, 2H, Cp ring-C*H*$_2$-cyclen ring), 3.98 (br, 3H, N*H*), 4.15 (s, 5H, C*H* Cp ring), 4.23 (m, 2H, C*H* Cp ring), 4.32 (m, 2H, C*H* Cp ring). ^{13}C NMR (DMSO-d_6): δ 42.04 (*C*H$_2$ cyclen ring), 43.56 (*C*H$_2$ cyclen ring), 44.32 (*C*H$_2$ cyclen ring), 48.85 (*C*H$_2$ cyclen ring), 52.37 (Cp ring-*C*H$_2$-cyclen ring), 68.42 (*C*H Cp ring), 68.56 (*C*H Cp ring), 70.65 (*C*H Cp ring), 77.47 (*C* Cp ring).

$[Zn(L)(Thymine\ anion)](ClO_4) \cdot 2H_2O$ (C4). Thymine (9 mg, 0.076 mmol) and **C1** (50 mg, 0.076 mmol) were dissolved in a mixture of water (5 mL) and acetonitrile (1 mL). The pH of the solution was adjusted to 9.5 with aqueous 0.1 M NaOH. The mixture was stirred at room temperature for 30 min. After the solvent had been evaporated, the solid was crystallized from water/ethanol to yield yellow plate crystals suitable for X-ray crystallography. Yield: 30 mg (53%). Anal. Found (%): C, 42.1; H, 5.6; N, 12.1. Calcd for $ZnFeC_{24}H_{35}N_6O_6Cl \cdot 2H_2O$ (%): C, 41.4; H, 5.6; N, 12.1. Major IR bands (KBr, ν, cm^{-1}): 3450 w br, 3297 w, 2923 m, 1737 w, 1719 m 1702 m, 1653 s, 1562 s, 1425 s, 1270 m, 1103 s, 971 s, 938 s, 897 m, 821 m 703 m, 625 m, 439 m. ^1H NMR (DMSO-d_6): δ 1.94 (s, 3H, C*H*$_3$ thymine), 2.62−3.22 (m, 13H, C*H*$_2$ cyclen ring), 3.40−3.52 (m, 1H, C*H*$_2$ cyclen ring), 3.57−3.70 (m, 2H, C*H*$_2$ cyclen ring), 3.81 (s, 2H, Cp ring-C*H*$_2$-cyclen ring), 4.23 (s, 5H, C*H* Cp ring), 4.31 (m, 2H, C*H* Cp ring), 4.36 (m, 2H, C*H* Cp ring), 7.41 (s, 1H, C*H* thymine). ^1H NMR (DMSO-d_6): δ 1.78 (s, 3H, C*H*$_3$ thymine), 2.45−2.89 (m, 14H, C*H*$_2$ cyclen ring), 2.90−3.05 (m, 2H, C*H*$_2$ cyclen ring), 3.70 (s, 2H, Cp ring-C*H*$_2$-cyclen ring), 3.89 (br, 2H, N*H*), 3.98 (br, 1H, N*H*), 4.05 (s, 5H, C*H* Cp ring), 4.18 (m, 2H, C*H* Cp ring), 4.23 (m, 2H, C*H* Cp ring), 7.19 (d, 1H, $^3J_{(CH,NH)} = 4.7$ Hz, C*H* thymine), 10.16 (d, 1H, $^3J_{(NH,CH)} = 4.7$ Hz, N*H* thymine). ^{13}C NMR (DMSO): δ 12.77 (*C*H$_3$ thymine), 42.10 (*C*H$_2$ cyclen ring), 43.68 (*C*H$_2$ cyclen ring), 44.21 (*C*H$_2$ cyclen ring), 48.89 (*C*H$_2$ cyclen ring), 51.03 (Cp ring-*C*H$_2$-cyclen ring), 68.34 (*C*H Cp ring), 68.48 (*C*H Cp ring), 70.71 (*C*H Cp ring), 77.70 (*C* Cp ring), 107.45 ((CO)(CH_3)−*C*═C), 136.90 (*C*H thymine), 158.00 (NH−*C*O−N), 172.35 (N−*C*O−C═C).

$[Zn(L)(Thymidine\ anion)](ClO_4) \cdot 3.5H_2O$ (C5). Thymidine (18 mg, 0.077 mmol) and **C1** (50 mg, 0.077 mmol) were dissolved in a 1:1 mixture of water (5 mL) and acetonitrile (1 mL). The pH of

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Table 1. Crystallographic Data

	C1	**C3**	**C4**
empirical formula	$C_{19}H_{32}Cl_2FeN_4O_9Zn$	$C_{21}H_{33}Cl_2FeN_5O_4Zn$	$C_{24}H_{39}ClFeN_6O_8Zn$
M (g mol^{-1})	652.63	611.67	696.30
cryst syst	monoclinic	orthorhombic	monoclinic
space group	$P2_1/n$	$Pnma$	$P2_1/c$
a (Å)	16.5906(6)	11.3576(7)	11.691(2)
b (Å)	9.3692(3)	9.2364(5)	14.152(3)
c (Å)	17.1718(5)	24.7717(14)	35.978(7)
β (deg)	110.166(2)	90	90.08(3)
V (Å^3)	2505.57(14)	2598.6(3)	5953(2)
Z	4	4	8
T (K)	123(2)	123(2)	123(2)
λ (Å)	0.71073	0.71073	0.71073
D_c (g cm^{-3})	1.730	1.638	1.543
μ(Mo Kα) (mm^{-1})	1.806	1.730	1.438
no. data measured	33 184	22 481	56 601
unique data (R_{int})	7347 (0.0443)	5666 (0.0293)	14179 (0.835)
obsd data [$I > 2(\sigma)I$]	6116	4719	9183
final R1, wR2 (obsd data)	0.0468,[a] 0.0906[b]	0.0801,[a] 0.1917[b]	0.0821,[a] 0.2008[b]
final R1, wR2 (all data)	0.0607, 0.0957	0.0963, 0.1996	0.1298, 0.2180
ρ_{min}, ρ_{max} (e Å^{-3})	−0.752, 1.398	−1.166, 1.726	−0.918, 1.142

[a] $R1 = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$. [b] $wR2 = [\Sigma w(|F_o| - |F_c|)^2/\Sigma F_o^2]^{1/2}$, where $w = [\sigma^2(F_o)]^{-1}$.

the solution was adjusted to 9.5 with aqueous 0.1 M NaOH. The mixture was stirred at room temperature for 30 min. After the solvent had been evaporated, the solid was dissolved in a 1:1 mixture of ethanol (3 mL) and acetone (3 mL), and diethyl ether was added until precipitation of the orange solid complex, which was filtered and air-dried. Yield: 52 mg (88%). Anal. Found (%): C, 41.2; H, 5.4; N, 9.4. Calcd for $ZnFeC_{29}H_{43}N_6O_9Cl{\cdot}3.5\ H_2O$ (%): C, 41.5; H, 5.9; N, 10.0. Major IR bands (KBr, ν, cm^{-1}): 3410 m br, 3302 m, 2927 w, 1656 m, 1577 s, 1445 m, 1367 w, 1294 m, 1094 s, 968 m, 784 w, 624 w. ^{1}H NMR (DMSO-d_6): δ 1.83 (s, 3H, $\mathrm{C}H_3$ thymine), 2.05 (m, 2H, $\mathrm{CH{-}C}H_2\mathrm{{-}CHOH}$), 2.50−3.00 (m, 16H, $\mathrm{C}H_2$ cyclen ring), 3.55 (m, $\mathrm{C}H_2\mathrm{{-}OH}$, 2H,), 3.70 (m, 3H, Cp ring-$\mathrm{C}H_2$-cyclen ring and $\mathrm{O{-}C}H\mathrm{{-}CH_2OH}$), 3.88 (s, 2H, NH), 3.95 (m, 1H, NH), 4.05 (s, 5H, $\mathrm{C}H$ Cp ring), 4.17 (m, 2H, $\mathrm{C}H$ Cp ring), 4.23 (m, 3H, $\mathrm{C}H$ Cp ring and $\mathrm{C}H\mathrm{{-}OH}$), 4.93 (m, 1H, $\mathrm{CH_2{-}O}H$), 5.18 (d, 1H, $^3J = 3.7$ Hz, $\mathrm{CH{-}O}H$), 6.33 (m, 1H, $\mathrm{N{-}C}H\mathrm{{-}O}$), 7.63 (s, 1H, $\mathrm{C}H$ thymine). ^{13}C NMR (DMSO-d_6): δ 13.17 ($C\mathrm{H_3}$ thymine), 39.50 ($\mathrm{CH{-}}C\mathrm{H_2{-}CHOH}$), 42.11 ($C\mathrm{H_2}$ cyclen ring), 43.68 ($C\mathrm{H_2}$ cyclen ring), 44.23 ($C\mathrm{H_2}$ cyclen ring), 48.91 ($C\mathrm{H_2}$ cyclen ring), 51.09 (Cp ring-$C\mathrm{H_2}$-cyclen ring), 61.51 ($C\mathrm{H_2{-}OH}$), 68.46 ($C\mathrm{H}$ Cp ring), 68.34 ($C\mathrm{H}$ Cp ring), 70.63 ($C\mathrm{H}$ Cp ring), 77.71 (C Cp ring), 84.06 ($\mathrm{N{-}}C\mathrm{H{-}O}$), 86.90 ($\mathrm{O{-}}C\mathrm{H{-}CH_2OH}$), 109.36 ($\mathrm{(CH_3){-}}C\mathrm{{=}C}$), 135.40 ($C\mathrm{H}$ thymine), 156.49 ($\mathrm{N{-}}C\mathrm{O{-}N}$), 171.05 ($\mathrm{C{-}}C\mathrm{O{-}N}$).

[NaZn(L)(Thymidine 5′-monophosphate anion)] (C6). **C1** (20 mg, 0.031 mmol) and thyminidine 5′-monophosphate disodium salt (TMP^{2-}) (11 mg, 0.031 mmol) were dissolved in a 1:1 mixture of water (5 mL) and acetonitrile (1 mL), and the pH was adjusted to 9.5 with aqueous 0.1 M NaOH. The mixture was stirred for 30 min at room temperature. The solvent was then removed in vacuo, and the residual solid was washed with ethanol several times and dried to give an orange solid that still contained inorganic salts. Major IR bands (KBr, ν, cm^{-1}): 3427 s br, 2925 m, 2880 m, 1659 m, 1576 m, 1466 m, 1368 w, 1294 w, 1089 s, 976 m, 629 w. ^{1}H NMR (DMSO-d_6): δ δ 2.00 (s, 3H, $\mathrm{C}H_3$ thymine), 2.43 (m, 2H, $\mathrm{C}H_2\mathrm{{-}CHOH}$), 2.62−3.22 (m, 13H, $\mathrm{C}H_2$ cyclen ring), 3.35−3.45 (m, 1H, $\mathrm{C}H_2$ cyclen ring), 3.53−3.68 (m, 2H, $\mathrm{C}H_2$ cyclen ring), 3.84 (s, 2H, Cp ring-$\mathrm{C}H_2$-cyclen ring), 4.01 (m, 2H, $\mathrm{C}H_2\mathrm{{-}OPO_3}$), 4.19 (m, 1H, $\mathrm{C}H\mathrm{{-}OH}$), 4.22 (s, 5H, $\mathrm{C}H$ Cp ring), 4.30 (m, 2H, $\mathrm{C}H$ Cp ring), 4.35 (m, 2H, $\mathrm{C}H$ Cp ring), 4.65 (m, 1H, $\mathrm{C}H\mathrm{{-}CH_2{-}OPO_3}$), 6.42 (m, 1H, N thymine-$\mathrm{C}H$ sugar), 7.80 (s, 1H, $\mathrm{C}H$ thymine). ^{13}C NMR (DMSO-d_6): δ 12.73 ($C\mathrm{H_3}$ thymine), 38.75 ($C\mathrm{H_2{-}CHOH}$), 42.64 ($C\mathrm{H_2}$ cyclen ring), 44.17 ($C\mathrm{H_2}$ cyclen ring), 44.77 ($C\mathrm{H_2}$ cyclen ring), 49.94 ($C\mathrm{H_2}$ cyclen ring), 52.64 (Cp ring-$C\mathrm{H_2}$-cyclen ring), 64.34 ($C\mathrm{H_2{-}OPO_3}$), 69.29 ($C\mathrm{H}$ Cp ring), 71.58 ($C\mathrm{H}$ Cp ring), 71.65 ($C\mathrm{H}$ Cp ring), 78.41 (C Cp ring), 85.28 (N thymine-$C\mathrm{H}$ sugar), 86.05 ($C\mathrm{H{-}OH}$), 86.22 ($\mathrm{C}H\mathrm{{-}CH_2{-}OPO_3}$), 112.17 ($\mathrm{CH_3{-}}C\mathrm{{=}C}$), 137.53 ($C\mathrm{H}$ thymine). Despite an increase of the relaxation time, two of the expected carbonyl carbons could not be observed. ^{31}P NMR (D_2O): δ 5.89 (s, $\mathrm{O}PO_3$).

X-ray Crystallography. Intensity data for **C1** (0.30 × 0.11 × 0.03 mm) and **C4** (0.15 × 0.10 × 0.09 mm) were measured at 123 K on a Nonius Kappa CCD fitted with a graphite-monochromated Mo Kα radiation (0. 71073 Å) source. Data for **C3** (0.49 × 0.20 × 0.08 mm) were measured on a Bruker Apex 2 CCD fitted with a graphite-monochromated Mo Kα radiation (0. 71073 Å) source. The data were collected to a maximum 2θ value of 55° (65° for **C3**) and processed using the Nonius software (Bruker Apex 2 software for **C3**) (collection and refinement parameters are summarized in Table 1). The structures were solved by direct methods and expanded using standard Fourier routines in the SHELX-97[14,15] software package. All hydrogens were placed in idealized positions, and all non-hydrogen atoms were refined anisotropically. The site occupancies for the nitrogen and carbon atoms in the cyclen rings of **C3** were refined in two distinct positions.

Results and Discussion

Synthesis of Ligand L and its Zn^{II} Complexes (C1, C2 and C3). The ligand 1-(ferrocenemethyl)-1,4,7,10-tetraazacyclododecane (**L**, Figure 1) was obtained following the general procedure published by Sisti et al.[13] Three different Zn^{II} complexes (**C1**, **C2**, and **C3**, Figure 1) were obtained by reaction of an equimolar mixture of **L** with $Zn(ClO_4)_2{\cdot}6H_2O$. If the pH was adjusted to 5 at the beginning of the synthesis, a complex in which a water molecule is coordinated to the Zn^{II} ion was obtained (**C1**). In contrast, if the pH was adjusted to 10, a hydroxide ion is coordinated to the Zn^{II} ion to give **C2**. Interestingly, during an attempt at

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(14) Sheldrick, G. M. *SHELXS97, Program for crystal structure solution*; University of Göttingen: Göttingen, Germany, 1997.

(15) Sheldrick, G. M. *SHELXL97, Program for crystal structure refinement*; University of Göttingen: Göttingen, Germany, 1997.

purification of **C2** using a Sephadex SP C25 cation-exchange column, complex **C3** was isolated and fully characterized. It is assumed that exchange of chloride for coordinated water must have occurred, probably via the presence of residual NaCl which was used during the loading of the column. The outcome highlights an interesting coordination preference of the Zn^{II} cation for chloride instead of hydroxide or water.

The formation of the three complexes was confirmed by shifts in the ^{1}H and ^{13}C NMR resonances (in DMSO-d_6) of the receptor protons and carbons which are the closest to the complexation site. An important change of about +0.24 ppm is observed for the CH_2 protons linking the cyclen to the ferrocenyl moiety upon complexation. The three amine protons of the cyclen ring undergo a general shift to higher frequencies. Interestingly, in the ^{1}H spectrum of complexes **C1** and **C2**, two different signals are observed for the N*H* protons, indicating the presence of the expected two types of N*H* protons. The integration is also consistent with the expected 2:1 ratio. In the case of **C3**, only one signal is observed at 3.98 ppm. In the ^{13}C NMR spectrum, the quaternary carbon of the ferrocene group undergoes a large shift to lower frequencies (>5.5 pm) when **L** is complexed to a Zn^{II} ion. IR spectroscopy shows characteristic bands at about 2930 and 3290 cm^{-1} corresponding to aromatic C−H stretching and N−H stretching, respectively, for each isolated ferrocenyl compound. The complexes **C1**, **C2**, and **C3** exhibited a strong resonance at about 1100 cm^{-1}, corresponding to Cl−O stretching of the perchlorate anions, but this band may also be indicative of the presence of monosubstituted ferrocene and is seen in the IR spectrum of the ligand **L**.[16] Definitive evidence of the formation of **C1**, **C2**, and **C3** was obtained by X-ray structural analysis as described below and the concordance of the microanalysis data with expected values.

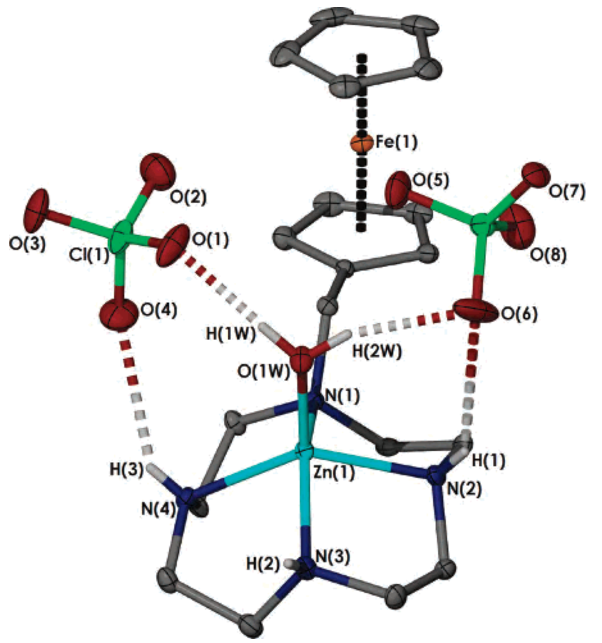

Figure 2. Thermal ellipsoid plot of the asymmetric unit (ASU) of **C1** (ellipsoids drawn at 50% probability). Some hydrogens are omitted for clarity.

Table 2. Selected Bond Distances (Å) and Bond Angles (deg) for **C1**[a]

Zn(1)−O(1W)	1.979(2)	O(1W)−Zn(1)−N(4)	117.55(9)
Zn(1)−N(4)	2.124(2)	O(1W)−Zn(1)−N(2)	103.81(9)
Zn(1)−N(2)	2.115(2)	O(1W)−Zn(1)−N(3)	106.26(9)
Zn(1)−N(3)	2.117(2)	O(1W)−Zn(1)−N(1)	112.20(8)
Zn(1)−N(1)	2.155(2)	N(3)−Zn(1)−N(1)	141.33(8)
		N(2)−Zn(1)−N(4)	138.56(9)
		N(4)−Zn(1)−N(3)	82.70(8)
		N(2)−Zn(1)−N(3)	83.50(8)
		N(4)−Zn(1)−N(1)	83.22(8)
		N(2)−Zn(1)−N(1)	83.68(8)

[a] ESD in parentheses.

X-ray Crystal Structure Determinations. The X-ray crystal structure of **C1** (Figure 2) reveals a Zn^{II} cation coordinated in a highly distorted geometry constructed from a base that is occupied by nitrogen donor atoms from the cyclen component of the ligand. An estimation of the degree of distortion using the method of Addison et al.[17] gave τ = 0.40, a value which indicates that the geometry is intermediate between square pyramidal (SP, $\tau = 0$) and trigonal bipyramidal (TBP, $\tau = 1$). The apical position of the coordination pyramid is occupied by a strongly coordinated water with a Zn−O distance of 1.979(2) Å (Table 2 gives distances and angles). The three NH groups are all directed in a cisoid orientation with respect to the coordinated water, which implies that little conformational change is necessary for the NH groups to undergo hydrogen bonding with the thymine ligand as found in **C4**. The ferrocene pendant has the two Cp rings in an eclipsed configuration, and the Fe center is 6.166(3) Å away from the Zn center. There is a noticeable displacement of the Zn center out of the plane formed by the four secondary cyclen nitrogens of 0.729(3) Å. This is not unexpected because previous Zn cyclen structures with water coordinated at the apical position move the Zn 0.766 Å from the basal coordination plane.[18]

To the best of our knowledge, only Kimura et al.[18] and Kong et al.[19] have reported an X-ray structure of a Zn^{II}-cyclen derivative, in which the Zn center is bound to only one water molecule and in which the Zn center is pentacoordinated. The Zn−O distances reported for these complexes are shorter than those found in **C1** (1.947 and 1.918 Å, respectively, compared to 1.979 Å in **C1**). Kimura et al. also described another complex in which the Zn ion is linked to the four nitrogens of the cyclen derivative, to an oxygen atom of a pendent alcohol arm of the cyclen, and to a water molecule and which has a Zn−O distance of 2.130 Å.[20] Rheingold et al. recently reported the structure of a Zn cyclen complex in which the Zn center is in a distorted octahedral environment and bound to two water molecules with Zn−O

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Table 3. Hydrogen Bonds for **C1** (Å and deg)[a]

D−H···A	d(D−H)	d(H···A)	d(D···A)	∠(DHA)
N(3)−H(2)···O(3)#1	0.81(3)	2.32(3)	3.058(3)	152(3)
N(4)−H(3)···O(4)	0.73(3)	2.47(3)	3.081(3)	142(3)
N(2)−H(1)···O(6)	0.80(3)	2.50(3)	3.156(3)	140(3)
N(2)−H(1)···O(7)#2	0.80(3)	2.52(3)	3.179(3)	141(3)
O(1W)−H(1W)···O(1)	0.80(4)	1.90(4)	2.701(3)	175(4)
O(1W)−H(2W)···O(6)	0.83(1)	2.05(2)	2.839(3)	159(4)
O(1W)−H(2W)···O(5)	0.83(1)	2.47(3)	3.106(3)	134(4)

[a] Symmetry transformations used to generate equivalent atoms: #1 $-x + 2, -y + 1, -z$; #2 $-x + 3/2, y - 1/2, -z + 1/2$.

distances of 2.122 Å.[21] These two last complexes, as expected, have longer Zn−O distances because of the octahedral coordination geometry. Interestingly, the X-ray structure shows that the coordinated water of **C1** participates in hydrogen bonding with the perchlorate counterions (Table 3 gives hydrogen-bonding distances and angles). The O(1W)−O(1) and O(1W)−O(6) distances of 2.701(3) and 2.839(3) Å, respectively, indicate moderate strength hydrogen bonding. For weak hydrogen-bond acceptors, such interactions are typified by O···O distances of ≥3.0 Å.[22−24] This suggests that the water is coordinated to the Zn center tightly and, as a consequence, is more acidic (pK_a = 7.36(9) vide infra) than water bound to related systems. Notably, for the parent Zn^{II}-cyclen complex, the pK_a of the coordinated water is reduced from 14.7 to 7.9,[2] but it is not reduced to the extent observed for **C1**. The other X-ray crystal structure showing this hydrogen-bonding motif in the literature was reported by Kimura et al., in which the water oxygen to perchlorate oxygen distances are 2.879 and 2.831 Å.[20] However, in this case, the Zn center was hexacoordinated, leading to a lower acidity of the coordinated water. In **C1**, both the perchlorate anions also form weak hydrogen bonds with the secondary nitrogens on the cyclen ring with heteroatom−heteroatom distances of 3.156(3) and 3.081(3) Å for N(2)−O(6) and N(4)−O(4), respectively, which essentially results in the generation of a seven-membered chelate ring.

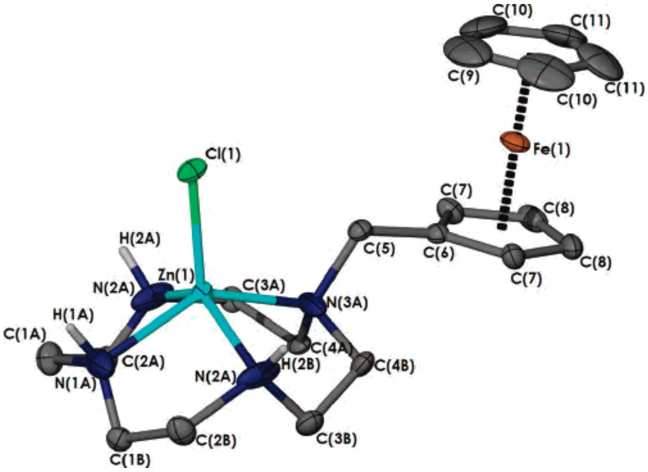

Figure 3. Thermal ellipsoid plot of **C3** (ellipsoids drawn at 50% probability). Some hydrogens, solvent molecules, and disorder are omitted for clarity.

Table 4. Bond Lengths (Å) and Angles (deg) for **C3**[a]

Zn(1)−N(2A)	2.123(3)	N(2A)−Zn(1)−N(1A)	82.15(1)
Zn(1)−N(1A)	2.124(5)	N(2A)#1−Zn(1)−N(1A)	82.15(1)
Zn(1)−N(3A)	2.175(5)	N(2A)−Zn(1)−N(3A)	81.97(1)
Zn(1)−Cl(1)	2.239(1)	N(2A)#1−Zn(1)−N(3A)	81.97(1)
		N(1A)−Zn(1)−N(3A)	137.44(2)
		N(2A)−Zn(1)−N(2A)#1	135.24(2)
		N(2A)−Zn(1)−Cl(1)	112.38(1)
		N(1A)−Zn(1)−Cl(1)	111.79(2)
		N(3A)−Zn(1)−Cl(1)	110.77(1)

[a] Symmetry transformations used to generate equivalent atoms: #1 $x, -y + 1/2, z$.

Table 5. Hydrogen Bonds for **C3** (Å and deg)[a]

D−H···A	d(D−H)	d(H···A)	d(D···A)	∠(DHA)
N(1A)−H(1A)···O(3P)#1	0.93	2.35	3.162(6)	146
N(1A)−H(1A)···O(3P)#2	0.93	2.35	3.162(6)	146
N(2A)−H(2A)···Cl(1)#3	0.93	2.41	3.282(4)	156
N(2B)−H(2B)···Cl(1)#3	0.93	2.56	3.282(4)	135

[a] Symmetry transformations used to generate equivalent atoms: #1 $x + 1, -y + 1/2, z$; #2 $x + 1, y, z$; #3 $-x + 2, -y, -z + 1$.

The X-ray crystal structure of **C3** presented in Figure 3 is broadly similar to that of **C1**, in the respect that the Zn center again adopts a geometry that is intermediate between square pyramidal and trigonal bipyramidal ($\tau = 0.42$) (bond angles and distance are listed in Table 4). The basal plane of the pyramid is coordinated by nitrogen donors from the cyclen macrocycle, and the apex of the pyramid is occupied by a chloride ligand (Zn−Cl = 2.239(1) Å). The out-of-plane distance of the Zn from the least-squares plane defined by the nitrogen donors in the cyclen is 0.794 Å, which is slightly larger than that found in **C1**. The Zn−Fe distance of 6.139(3) Å is similar to that found in **C1**, and the Cp rings also exist in an eclipsed geometry. Only half the molecule exists in the ASU (with a cocrystallized molecule of acetonitrile), and the cyclen ring is disordered across two distinct positions, each with a 50% occupancy.

C3 is only the second example of a complex that has a Zn^{II} center bound to the four cyclen nitrogen atoms and a chloride.[25] Kobayashi found a Zn−Cl distance of 2.24 Å, which is similar to that found in **C3**. Hubin et al.[26] reported a complex in which the Zn ion was bound to two chloride ligands and four nitrogens from a cyclen derivative. In this complex, the Zn−Cl distance is much longer than in **C3** (2.376 vs 2.239(1) Å in **C3**). An interesting feature of **C3** is the hydrogen-bonding network (Table 5 and Figure 4) between adjacent molecules, formed by interactions between the secondary amine hydrogen atoms of the cyclen ring and chloride ligands on neighboring molecules (viz., N···Cl = 3.282(4) Å). The remaining amine hydrogen bonds to the perchlorate anion with a N···O distance of 3.162(6) Å, slightly longer than the hydrogen bond between the cyclen

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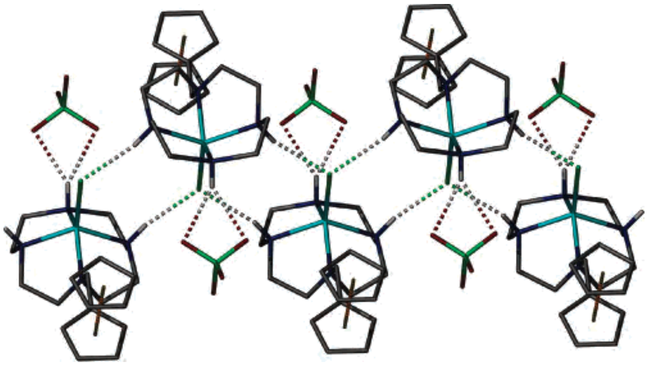

Figure 4. Stick representation of **C3** showing hydrogen bonding between adjacent complexes (dashed lines).

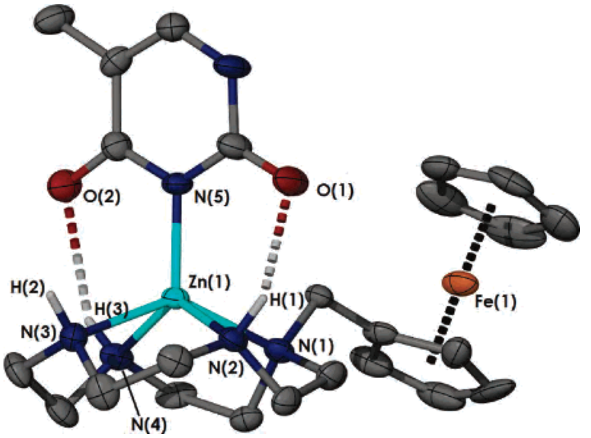

Figure 5. Thermal ellipsoid plot of the complex cation of **C4** (ellipsoids drawn at 50% probability). The second cation in the ASU, perchlorate anions, selected hydrogens, and H_2O molecules are omitted for clarity.

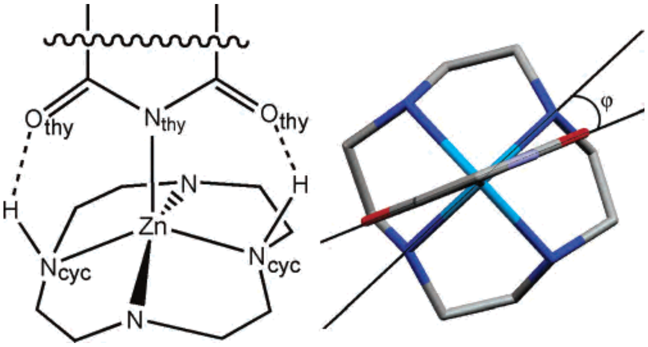

Figure 6. Illustration of various important geometrical features of the (Zn-cyclen)−thymine interaction: (left) coordination and hydrogen bonding of thymine and (right) top view illustrating angle between plane of the thymine and the cyclen's N−Zn−N.

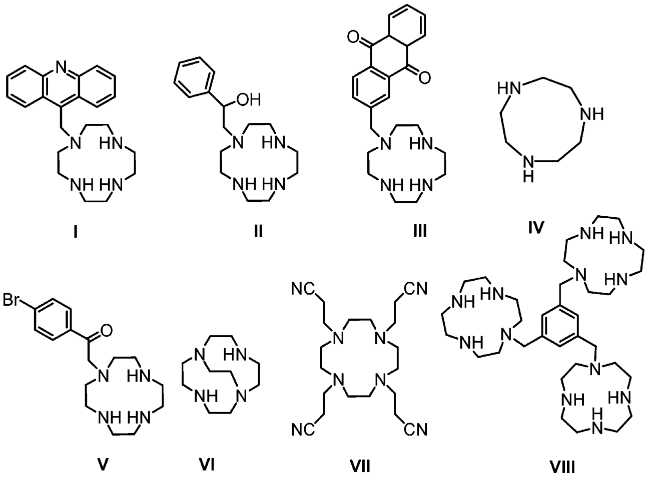

Figure 7. Structures of ligands in Table 9.

Table 6. Selected Bond Distances (Å) and Bond Angles (deg) of **C4**^{a}

cation 1		cation 2	
Zn(1)−N(1)	2.218(6)	Zn(2)−N(7)	2.221(5)
Zn(1)−N(2)	2.104(5)	Zn(2)−N(8)	2.108(5)
Zn(1)−N(3)	2.190(6)	Zn(2)−N(9)	2.157(6)
Zn(1)−N(4)	2.122(5)	Zn(2)−N(10)	2.110(5)
Zn(1)−N(5)	1.975(5)	Zn(2)−N(11)	1.979(5)
O(1)−C(20)	1.266(9)	O(3)−C(44)	1.236(8)
O(2)−C(23)	1.251(8)	O(4)−C(47)	1.252(8)
N(5)−C(20)	1.353(9)	N(11)−C(44)	1.333(9)
N(5)−C(23)	1.367(9)	N(11)−C(47)	1.396(8)
N(2)−Zn(1)−N(1)	80.2(2)	N(8)−Zn(2)−N(7)	81.2(2)
N(2)−Zn(1)−N(3)	81.3(2)	N(8)−Zn(2)−N(9)	81.9(2)
N(2)−Zn(1)−N(4)	131.4(2)	N(8)−Zn(2)−N(10)	130.9(2)
N(3)−Zn(1)−N(1)	137.4(2)	N(9)−Zn(2)−N(7)	137.8(2)
N(4)−Zn(1)−N(1)	82.5(2)	N(10)−Zn(2)−N(7)	81.2(2)
N(4)−Zn(1)−N(3)	81.6(2)	N(10)−Zn(2)−N(9)	81.3(2)
N(5)−Zn(1)−N(1)	113.4(2)	N(11)−Zn(2)−N(7)	108.9(2)
N(5)−Zn(1)−N(2)	109.5(2)	N(11)−Zn(2)−N(8)	114.8(2)
N(5)−Zn(1)−N(3)	108.9(2)	N(11)−Zn(2)−N(9)	113.2(2)
N(5)−Zn(1)−N(4)	119.1(2)	N(11)−Zn(2)−N(10)	114.3(2)

^{a} ESD in parentheses.

Table 7. Hydrogen Bonds for **C4** (Å and deg)

D−H···A	d(D−H)	d(H···A)	d(D···A)	∠(DHA)
N(2)−H(1)···O(1)	0.93^a	2.24	2.943(7)	131.8
N(4)−H(3)···O(2)	0.93^a	2.56	3.123(8)	119.7
N(8)−H(35)···O(3)	0.93^a	2.30	2.959(7)	127.3
N(8)−H(35)···O(7)	0.93^a	2.26	2.985(8)	134.2
N(10)−H(37)···O(4)	0.93^a	2.35	3.024(8)	129.1

^{a} Calculated positions.

amine and perchlorate in **C1** (vide supra). In **C3**, the perchlorate hydrogen bonds in a symmetrical "chelating" manner, with O(3P)$^{\#1}$ and O(3P)$^{\#2}$, forming a 3-membered chelate ring about H(1A) (symmetry operators #1 and #2 are defined by $x + 1$, $-y + 1/2$, z and $x + 1$, y, z, respectively).

An X-ray structure determination of **C4** revealed the presence of two crystallographically inequivalent complex cations (Figure 5). In this case, the Zn centers adopt a geometry that is much closer to trigonal bipyramidal ($\tau =$ 0.92, 0.93) when compared with **C1** and **C3**. One equatorial coordination site is occupied by the deprotonated "imine" nitrogen of thymine and the other two by cyclen secondary amines. The axial sites are occupied by the tertiary amine and the remaining secondary amine of the ligand. Of particular note are the short $Zn-N^-$ distances of 1.975(5) and 1.979(5) Å which are affected by hydrogen bonding between the thymine anion and the Zn cation. These distances are similar to those found in related compounds (Tables 6 and 8). Additional evidence of the strong binding of thymine is that the out of basal plane displacement of the Zn cation increases to 0.832(3) and 0.835(3) Å (0.05 Å more than in **C1** and **C3**). Interestingly, there is an elongation of 0.1 Å along the Zn−N bond that has the ferrocene pendent arm that is not as evident in the parent complex (**C1**). This indicates that the presence of the thymine anion forces the ferro-

Table 8. Comparison of **C4** with other Zn^{II}-cyclen−Thymine Complexes

compound	$Zn-N_{thy}$ (Å)	φ (deg)	$N_{cyc}-O_{thy}$ (Å)	ref
C4	1.975(5), 1.979(5)	26.44(21), 20.84(15)	2.943(7), 3.123(8)	this work
$[Zn^{II}$-[12]ane$N_4][AZT](ClO_4)\cdot 2H_2O$[a]	2.055, 1.902	43.62, 56.98	3.340, 3.340	2
$[Zn^{II}$-[12]aneN_4-acridine][MeThy]$(ClO_4)\cdot 2H_2O$[b]	1.987	30.49	2.881, 3.406	5
$[Zn^{II}$-[12]aneN_4-bis(MeNapthyl)][MeThy]$(NO_3)\cdot 2H_2O$[c]	1.979	27.01	3.156, 3.019	28

[a] (1,4,7,10-Tetra-azacyclododecane)-(3′-azido-3′-deoxythymidine-N^3)-zinc(II)$(ClO_4)\cdot 2H_2O$. [b] (1-Acridin-9-ylmethyl-1,4,7,10-tetra-azacyclododecane-*N*,*N*′,*N*′′,*N*′′′)-(N3-dehydro-1-methylthymine-N)-zinc(II)$(ClO_4)\cdot 2H_2O$. [c] (1,7-Bis(1-naphthylmethyl)-1,4,7,10-tetra-azacyclododecane)-(1-methylthymine)-zinc(II)$(NO_3)\cdot 2H_2O$.

Table 9. Comparison of the Deprotonation Constants (pK_a) and Zn−O Distances for Water Coordinated to **C1** and Related Compounds at 25 °C

complex	pK_a	Zn−O (Å)	ref
C1	7.36 ± 0.09[a]	1.979(2)	this work
cyclen	7.86[b]	*e*	6
Zn^{II}-acridine-pendent-cyclen (**I**)	7.5[b]	*e*	5
Zn^{II}-benzyl alcohol-pendent-cyclen (**II**)	7.51[b]	*e*	29
Zn^{II}-anthraquinone-pendent-cyclen (**III**)	7.48[c]	*e*	6
Zn^{II}−1,4,7-triazacyclododecane (**IV**)	7.30[d]	*e*	30
Zn^{II}-bromophenacylcyclen (**V**)	8.41[b]	2.130(3)	20
Zn^{II}-cis-diaqua-(1,4,7,10-tetra-azabicyclo(5,5,2)tetradecane) (**VI**)	*e*	2.123(4)	21
Zn^{II}−1,4,7,10-tetrakis(2-cyanoethyl)-cyclen (**VII**)	*e*	1.918(4)	19
Zn^{II}−1,3,5-tris(cyclen)−1-ylmethyl)benzene (**VIII**)	6.08, 7.25, 8.63	1.947(9)	18

[a] $I = 0.10$ M (KNO_3). [b] $I = 0.10$ ($NaClO_4$). [c] $I = 0.10$ M ($NaNO_3$). [d] $I = 0.20$ M ($NaClO_4$). [e] Not available.

cene moiety to bend away from the plane of the macrocycle, forcing the metal center to adopt a trigonal bipyramidal geometry. A slight elongation of the C−O bonds of the carbonyls is observed relative to thymine itself [(1.246(15) and 1.193(14) Å] compared to the four distances [1.266(9), 1.251(8), 1.236(8), and 1.252(8) Å] found in **C4**.[27] This corroborates with a lowering of the νC═O frequency in the IR spectrum.

The NH groups on the cyclen ring hydrogen bond to the carbonyl oxygen atoms on the thymine anion (Table 7). The hydrogen-bonding distances between the cyclen nitrogen and the carbonyl oxygen have an average value of 3.01 Å, indicating a moderate level of interaction. On average, these bonds are shorter than that found in other examples of thymine bound to Zn-cyclen.

An interesting feature of the bound thymine is that the calculated least-squares plane through the thymine is offset with respect to that passing through the $N_{cyclen}-Zn-N_{cyclen}$. This result is somewhat unexpected because to maximize the hydrogen-bonding potential it would be anticipated that they would lie in the same plane. This structural feature is illustrated in Figure 6. In fact, in the other compounds reported by Kimura et al.,[2,5,28] the Zn-cyclen−thymine interactions lead to an offset in the intersection of these two planes, φ (for comparison see Table 8).

It has been previously proposed that the hydrogen bonding of the complementary NH donors on the macrocycle to the carbonyl groups on the thymine add to the stability of the resulting complex.[3] While this is true and hydrogen bonding is present in all these complexes, some are quite weak, being as long as 3.41 Å (Table 8). If the hydrogen-bonding interactions were a dominant feature for binding, then all the φ angles would be expected to be close to zero. However, as can be seen in Table 8, all the φ angles are significantly greater than 20°, leading to weakening in hydrogen bonding. Even though the resulting coordinate bond between the negatively charged imide nitrogen and the Zn cation is strong and is the primary determinant of the stability of the adduct, the hydrogen bonds enhance stability of the complex and play an important role in the recognition of the correct complementary base by the metal complex. As a consequence, Kimura initially suggested that guanidine (dG) does not bind the Zn^{II}-cyclen receptor at all because there is a repulsive interaction between the two protons of the amine of dG and one of the NH groups of the cyclen macrocycle.[2] However, the same group subsequently reported an X-ray structure showing the binding of dG to a Zn^{II}-cyclen derivative receptor via a different mode of complexation.[5] In this case, the Zn ion is coordinated to the N(7) nitrogen and one N*H* proton hydrogen bonds the oxygen atom of the carbonyl function of dG. Furthermore, the affinity is also increased by the $\pi-\pi$ interactions between dG and the acridine arm of the ligand.[5]

Determination of pK_a of C1. pH titrations revealed that the pK_a of the coordinated water molecule is 7.36 ± 0.09 (see Experimental Section for details of the determination). This value indicates that **C1** is more acidic than the other mononuclear Zn(II)-cyclen analogues (see Table 9 and Figure 7 for the structures of the ligands). Table 9 also summarizes the Zn−O(water) distances determined by X-ray crystallography for **C1** and related complexes. It is interesting to note that Kimura et al. found that the coordinated water on their Zn^{II} complex of bromophenacylcyclen is less acidic (8.41 compared to 7.36 for **C1**) and exhibited a longer Zn−O distance (2.130 Å compared to 1.979 Å for **C1**).[20] As anticipated, a shorter Zn−O distance leads to a more acidic

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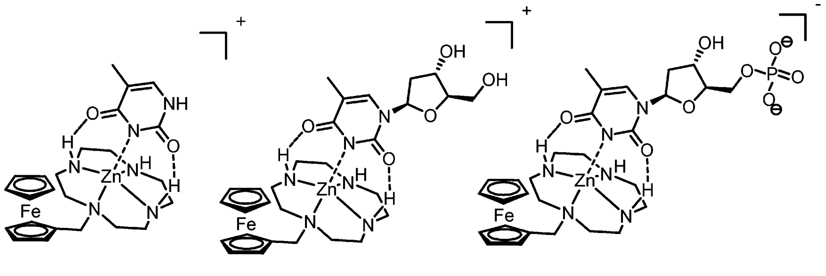


C4: [Zn(**L**)(T)][ClO$_4$] **C5**: [Zn(**L**)(dT)][ClO$_4$] **C6**: [Zn(**L**)(TMP)]$^-$

Figure 8. Structures of **C4**, **C5**, and **C6**.

Table 10. Comparison of Selected IR Stretches (cm^{-1}) in **C1** Adducts

	T	C4	dT	C5	TMP^{2-}	C6
νC=O (cm^{-1})	1736	1653	1703	1653	1698	1659
νC=C (cm^{-1})	1675	1562	1661	1577	1671	1576

complex. The trinuclear [Zn_3(1,3,5-tris(cyclen)-1-ylmethyl)-benzene)$(OH_2)_3$]$^{6+}$ complex shows higher acidity than **C1** because of the significantly higher overall charge and shorter Zn−O distance (1.947 Å compared to 1.979 Å in **C1**).[18] Consequently, the first two pK_a values are lower than what was found for **C1** (6.08 and 7.25 compared to 7.36).

Adduct Formation between Receptor C1 and Thymine (T), Thymidine (dT), and Thyminidine 5′-Monophosphate (TMP^{2-}) Anions. The reaction of **C1** with equimolar amounts of T, dT, and TMP^{2-} in aqueous solution at pH 9.5 afforded the complexes **C4**, **C5**, and **C6**, respectively, as shown in Figure 8.

IR spectroscopy (Table 10) reveals that a lowering of the C=O and C=C stretching frequencies of the thymine derivatives occurs upon complexation with **C1**, reflecting a weakening of the carbonyl and C=C double bonds caused by the deprotonation of the N(3)−H group and coordination of N(3). Further evidence of the elongation of the C=O bonds is provided in the X-ray structure discussion of **C4** (see above). The agreement in the $\nu_{C=O}$ and $\nu_{C=C}$ stretches for the **C1** adducts with T, dT, and TMP^{2-} provides definitive evidence that TMP^{2-} binds to the Zn^{2+} ion through the thymine base and not through the phosphate group.

Further evidence of the formation of the complexes is provided by the shift in the ^{1}H and ^{13}C NMR spectra measured in DMSO-d_6. Furthermore, the deprotonation of the N−H group of the thymine ring in each **C4**, **C5**, and **C6** is supported by the lack of the imide proton N(3)−H of T, dT, and TMP^{2-} in the ^{1}H NMR spectra. Interestingly, similar to **C1** and **C2**, two types of ^{1}H NMR signals at $\delta = 3.98$ (br, 1H) and 3.89 (br, 2H) for **C4** and $\delta = 3.95$ (br, 1H) and 3.88 (br, 2H) for **C5** are detected for the N*H* protons of the cyclen and are attributed to the presence of two different kinds of NH protons. Unfortunately, the expected analogous feature for **C6** could not be detected because of its insolubility in DMSO-d_6. The N*H* peaks are shifted to lower frequencies by about 0.3 ppm compared to those of **C1**, consistent with the fact that the amine protons are hydrogen bonded to the carbonyl of the thymine derivatives.

Electrochemical Studies. To assess the suitability of the ferrocene component of the receptor couple **C1**/**C2** as a redox sensor, voltammetric monitoring of changes that occur upon addition of an excess of thymine derivatives (dT and TMP^{2-}) was undertaken in buffer solution (MOPS) at pH 7.4. The electrochemical behavior of the Zn^{II} complexes of **L** in aqueous buffered solution can be described via a square scheme (Scheme 1).

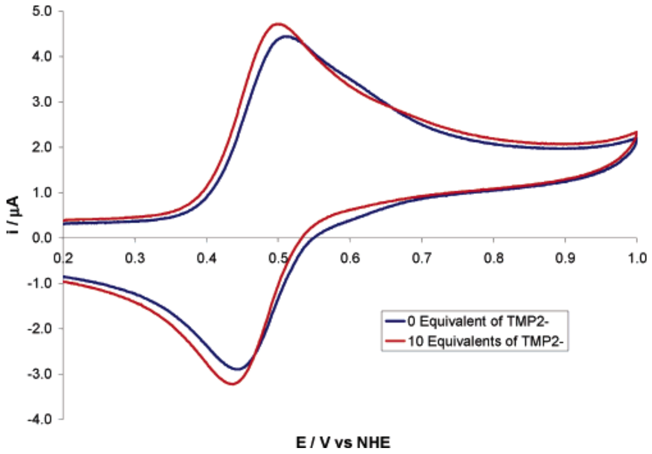
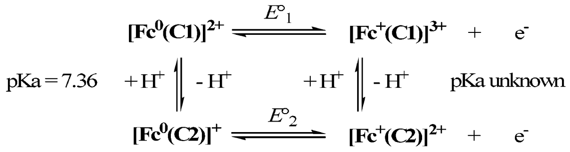


Figure 9. Cyclic voltammograms obtained at a scan rate of 25 mV s^{-1} for the receptor couple **C1**/**C2** (1 mM) at a GC electrode in the absence and presence of a 10 mol equiv of TMP^{2-} in an aqueous MOPS buffer solution at pH 7.4.

Scheme 1. Electrochemically Relevant Square Scheme Equilibria Established in Solutions of **C1**



The binding of the receptor couple **C1**/**C2** with different DNA nucleotides was followed by cyclic voltammetry in aqueous buffered solution at pH 7.4. The substrate was added in a 10-fold concentration excess to ensure full complexation of the thymine derivatives to the reduced form of the receptor. Cyclic voltammograms of the receptor and the complex formed upon the addition of an excess of TMP^{2-} are presented in Figure 9.

In the absence of the thymine derivatives, a major oxidation process exhibiting a reversible potential of 488 mV vs NHE (average of oxidation and reduction peak potentials) is detected. This process is followed by a barely detectable minor process with a reversible potential of about 600 mV vs NHE. Upon addition of TMP^{2-}, the minor process is removed, and a simple reversible process with an E_f° value of 478 mV vs NHE is detected. The small negative shift of E_f° is probably related to the replacement of the neutral water molecule of **C1** by the negatively charged thymidine monophosphate to form **C6**. **C6** is negatively monocharged compared to the double positively charged complex **C1**. This replacement is expected to make oxidation of the $Fc^{0/+}$ redox couple easier and corroborates our previous finding with a similar ligand that small changes in the $Fc^{0/+}$ redox couple occur in acetonitrile upon the addition of T.[8] The addition of dT and dG also gives rise to subtle rather than large changes in the voltammetry. However, the presence of the minor process and changes in the characteristics of the voltammograms upon addition of TMP^{2-} imply that the voltammetry in water is complex and that more experiments are needed to provide a detailed understanding of all the nuances. Importantly, the data indicate that the system is not likely to be useful as a voltammetric sensor at physiological pH.

Conclusions

We have prepared a cyclen derivative bearing a ferrocenyl moiety that can act as a nucleobase receptor. An examination of the Zn^{II} coordination chemistry of the receptor was undertaken, including X-ray structure determination of a number of complexes. In the aqua complex, **C1**, the coordinated water participates in hydrogen bonding with the perchlorate counterions. The pK_a value of the deprotonation of the water molecule determined by potentiometric titration was found to be 7.36 ± 0.09 at 25 °C and $I = 0.1$ (KNO_3); it is significantly lower than that for the parent [Zn-cyclen] complex. NMR and IR spectroscopy have shown that the Zn^{II} complex can bind thymine derivatives. The X-ray structure of the thymine complex **C4** confirmed that the ferrocenyl arm does not hinder the binding of thymine to the receptor, as evidenced by the short Zn−N(thymine) distance of 1.975(5) Å. The redox response is complex, and only small changes in potential are observed on addition of thymine derivatives under physiological conditions of pH.

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Supporting Information Available: Crystallographic data for **C1**, **C3** and **C4** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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