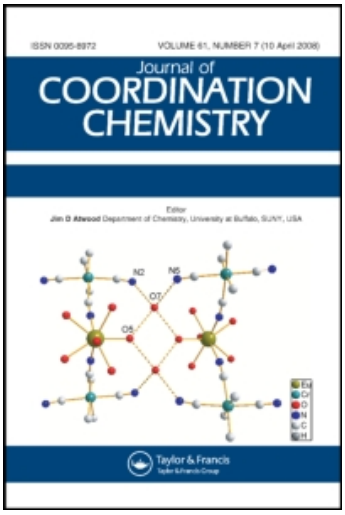

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A supramolecular optic receptor for selective recognition CDP in neutral aqueous solution

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A supramolecular optic receptor for selective recognition CDP in neutral aqueous solution

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We designed and synthesized a Cu-coordination complex based on a seven-membered amide cycle and studied its binding ability with nucleotides (cytidine 5′-monophosphate (CMP), cytidine 5′-diphosphate (CDP), cytidine 5′-triphosphate (CTP), cytidine d-5′-monophosphate (dCMP), and thymidine d-5′-monophosphate (dTMP)) by UV-Vis spectroscopy. Results indicate that the compound shows the highest binding ability with CDP among the studied nucleotides and can selectively and strongly bind nucleotides in neutral aqueous solution. The compound can be used as optical receptor for the detection of CDP.

Keywords: Optic receptor; Nucleotides; Recognition; Supramolecular interaction

1. Introduction

In recent years, increasing attention in the field of host–guest chemistry has been devoted to the development of anion recognition systems [1–7]. Detection of nucleotides is of paramount importance as they form the fundamental units of all life forms [8–12]. Most of the molecular receptors for nucleosides use complementary hydrogen bonding, but such recognition in aqueous medium would be limited due to the interference from hydroxyl groups of the sugar and competitive hydrogen bonding of the solvent [13–15]. Moreover, the sugar moiety of nucleosides can interfere in such recognition, and masking of hydroxyl groups prior to the recognition event is essential [16]. Progress in this area requires new strategies for selective recognition and subsequent signaling of the event under physiological pH.

In previous reports, recognition of adenosine was focused on supramolecular catalysis at certain pH [17, 18]. Recognition of ATP has been reported due to the important role of ATP in transporting chemical energy within cells for metabolism [16, 19–21]. Of all the nucleosides, recognition of cytidine 5′-monophosphate (CMP), cytidine 5′-diphosphate (CDP), cytidine 5′-triphosphate (CTP), cytidine d-5′-monophosphate (dCMP), and thymidine d-5′-monophosphate (dTMP) is vital [22–26]. In this

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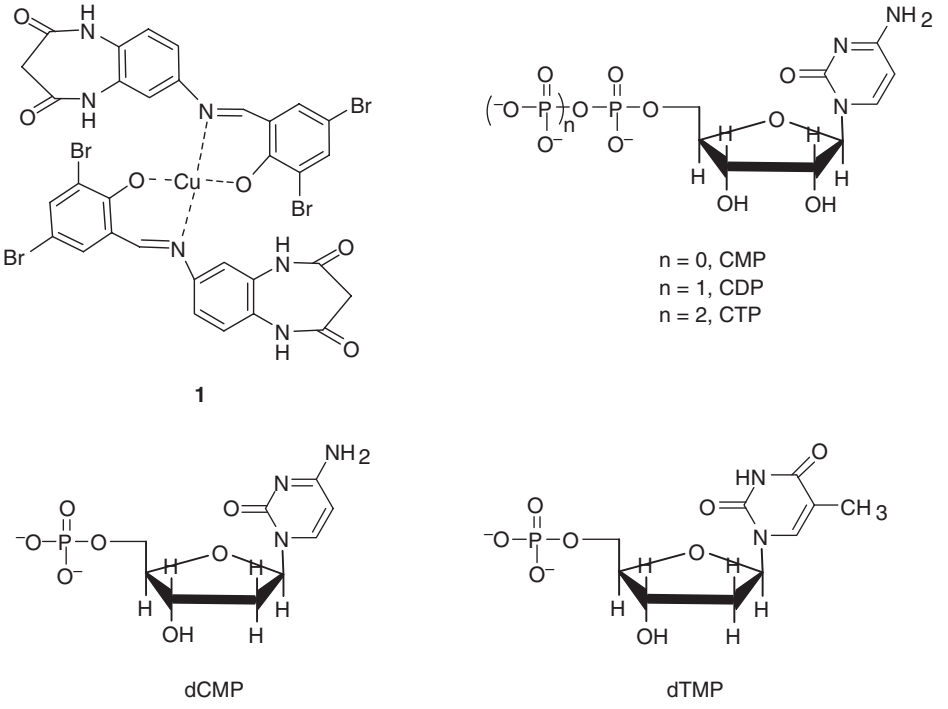


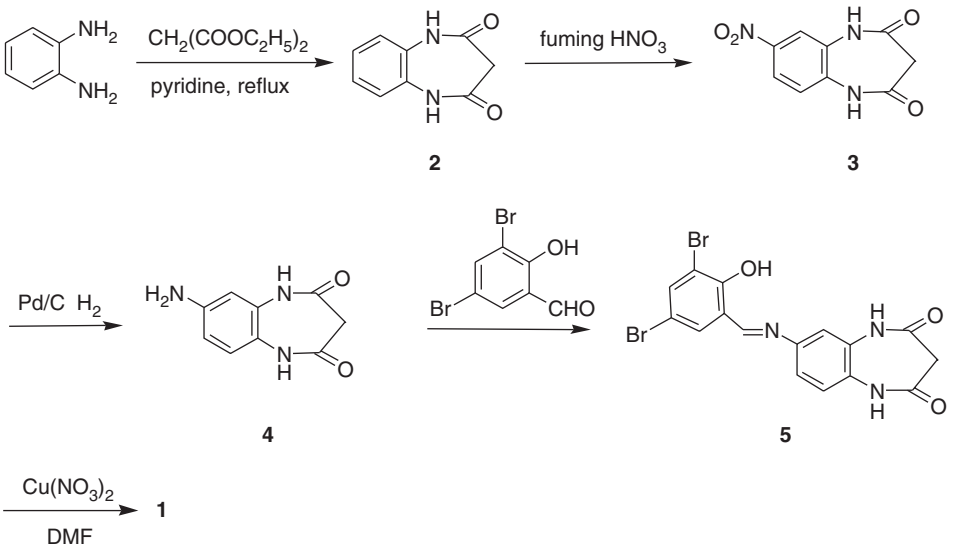
Scheme 1. Chemical structures of **1** and nucleotides.

article, we have reported the recognition of adenosine (CMP, CDP, CTP, dCMP, and dTMP) in neutral aqueous solution. A seven-membered compound, **1** (scheme 1), was synthesized and can interact with CMP, CDP, CTP, dCMP, and dTMP. Herein, we report the interaction of **1** with CMP, CDP, CTP, dCMP, and dTMP and selective complexation with CDP in aqueous solution with detection by changes in absorption spectroscopy.

2. Experimental

Most of the starting materials were obtained commercially and all reagents and solvents employed were of analytical grade. CMP, CDP, CTP, dCMP, and dTMP were purchased from Sigma-Aldrich Chemical Co., stored in a desiccator under vacuum containing self-indicating silica, and used without purification. Dimethyl sulfoxide (DMSO) was distilled *in vacuo* after drying with CaH_2. The elemental analysis of C, H, and N was made on a Vario-EL. ^{1}H NMR spectra were recorded on a Varian UNITY Plus-400 MHz spectrometer. FAB-MS was made on a VG ZAB-HS. UV-Vis spectroscopic titrations were made on a Shimadzu UV2450 spectrophotometer at 298 K. Stability constants K_s were obtained by non-linear least squares calculation through data fitting.

Compound **1** was synthesized according to the method shown in scheme 2.



Scheme 2. Synthesis for **1**.

2.1. *Benzo-1,4-diazacycloheptane[2,3-d]-5,7-dione (2)*

1,2-Phenylenediamine (10.8 g, 0.1 mol), diethyl malonate (16 mL, 0.1 mol), and pyridine (200 mL) were put in a 250 mL three-neck flask [27]. The mixture was refluxed with N_2 for 72 h. After cooling, the mixture was filtered giving a colorless solid. The solid was washed with ethanol and ether sequentially, and dried in vacuum. Yield: 72%. ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ 10.38 (s, 2H), 7.11–7.18 (m, 4H), 3.17 (s, 2H). Elemental analysis: Anal. Calcd for $C_9H_8N_2O_2$ (%): C, 61.4; H, 4.6; N, 15.9; Found (%): C, 61.7; H, 4.6; N, 16.0. FAB-MS (m/z): 177 $(M+H)^+$.

2.2. *(4′-Nitrobenzo)[1′,2′-d]-1,4-diazacycloheptane[2,3-d]-5,7-dione (3)*

Benzo-1,4-diazacycloheptane[2,3-d]-5,7-dione (10 mmol, 1.7 g) was dissolved in concentrated H_2SO_4 (43 mL). Fuming HNO_3 (1.1 mL) was added dropwise with stirring at 273 K. After addition was complete, the mixture was stirred for 2 h and then poured into *ca* 200 mL ice water. The solution was filtered to give a yellow solid which was washed with distilled water, recrystallized from methanol, and dried in vacuum. Yield: 85%. ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ 10.96 (s, 1H), 10.74 (s, 1H), 8.04, 7.3 (3H), 3.3 (s, 2H). Elemental analysis: Anal. Calcd for $C_9H_7N_3O_4$ (%): C, 48.9; H, 3.2; N, 19.0; Found (%): C, 48.8; H, 3.6; N, 18.6.

2.3. *(4′-Aminobenzo)[1′,2′-d]-1,4-diazacycloheptane[2,3-d]-5,7-dione (4)*

A slurry of (4′-nitrobenzo)[1′,2′-d]-1,4-diazacycloheptane[2,3-d]-5,7-dione (221 mg) and Pd/C (10%, 70 mg) in dry ethanol (200 mL) was maintained under hydrogen with stirring for 12 h. The mixture was filtered through a bed of Celite and then washed twice

with ethanol (2 × 20 mL). The solvents were removed under reduced pressure and the yellowish solid was dried in vacuum. Yield: 92%. ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ 10.15 (s, 1H), 9.91 (s, 1H), 6.76 (d, 1H), 6.38 (m, 1H), 6.27 (d, 2H), 5.16 (s, 2H), 3.08 (s, 2H). Elemental analysis: Anal. Calcd for $C_9H_9N_3O_2$ (%): C, 56.5; H, 4.7; N, 22.0; Found (%): C, 56.4; H, 5.0; N, 21.9.

2.4. *N-(2″-hydroxyl-3″,5″-dibromophenyl-methylene-yl)-4′-imino-benzo[1′,2′-d]-1,4-diazacycloheptane[2,3-d]-5,7-dione [HODBrphC=NphDNHexDO] (5)*

(4′-Aminobenzo)[1′,2′-d]-1,4-diazacycloheptane[2,3-d]-5,7-dione (1 mmol, 191 mg) and 3,5-dibromo-salicylaldehyde (1 mmol, 278 mg) were suspended in dry ethanol (100 mL). The mixture was heated under reflux for 8 h and the orange-yellow precipitate was separated by filtration. The solid was washed with diethyl ether and dried under vacuum. Yield: 89%. ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ 14.41 (s, 1H), 10.54 (s, 2H), 8.97 (s, 1H), 7.9 (d, 2H), 7.3 (d, 2H), 7.2 (m, 1H), 3.24 (s, 2H). Elemental analysis: Anal. Calcd for $C_{16}H_{11}N_3O_3Br_2$ (%): C, 42.4; H, 2.5; N, 9.3; Found (%): C, 42.4; H, 2.7; N, 9.5.

2.5. *Cu(II)[HODBrphC=NphDNHexDO]$_2$ (1)*

Compound **5** (0.1 mmol) and $Cu(NO_3)_2$ (0.05 mmol) were stirred for 1 h in DMF (20 mL), then kept at room temperature. After 1 month, green crystals appeared. Elemental analysis: Anal. Calcd for $C_{32}H_{20}N_6O_6Br_4Cu2DMF$ (%): C, 41.0; H, 3.1; N, 10.1; Found (%): C, 41.1; H, 3.1; N, 10.0.

2.6. *X-ray crystallography*

A green crystal of **1** with dimensions $0.20 \times 0.14 \times 0.06\,mm^3$ was mounted on a glass fiber. X-ray single-crystal diffraction data were collected on a Rigaku Saturn CCD area detector at 294(2) K with Mo-Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods and refined on F^2 by full-matrix least squares with SHELXL-97 [28]. Details of the crystallographic determination are given in table 1.

3. Results and discussion

Compound **1** was obtained by reaction of **5** and $Cu(NO_3)_2$ in DMF and the structure has been confirmed (figure 1, deposition number is CCDC 621069). The overall coordination environment of Cu(II) involves two **5**'s and two DMFs (the ORTEP image involves half of the crystal structure due to its symmetrical structure). Four, Cu1–O1, Cu1–O1A, Cu1–N1, and Cu1–N1A, bonds are relatively longer (bond lengths 1.913, 1.914, 2.033, and 2.033 Å) and constitute a planar quadrangular geometry around Cu(II) (O1–Cu1–O1A, 180°, O1–Cu1–N1, 90.7°, O1–Cu1–N1A, 89.3°, O1A–Cu1–N1, 89.3°, O1A–Cu1–N1A, 90.7°, and N1–Cu1–N1A, 180°); the other two, Cu–O4 and Cu–O4A, contacts are significantly shorter (bond lengths 1.653 and 1.653 Å),

Table 1. Crystallographic data of **1**.

Empirical formula	$C_{44}H_{48}Br_4CuN_{10}O_{10}$
Formula weight	1260.10
Temperature (K)	294(2)
Crystal system	Monoclinic
Space group	P_21/n
Unit cell dimensions (Å, °)	
a	12.035(2)
b	8.9193(14)
c	23.017(4)
α	90
β	94.422(5)
γ	90
Volume (Å^3), Z	2463.4(7), 2
Calculated density (g cm^{-3})	1.699
F (000)	1262
Crystal size (mm^3)	$0.20 \times 0.14 \times 0.06$
2θ range for data collection (°)	1.77–27.46
Reflections collected	20,636
R_{int}	0.0619
Data/restraints/parameters	5613/0/326
Goodness-of-fit F^2	1.020
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0522$, $wR_2 = 0.1067$
R indices (all data)	$R_1 = 0.0856$, $wR_2 = 0.1220$
Largest difference peak and hole (e Å^{-3})	0.607 and −0.657
Extinction coefficient	0.0022(4)

Weight $= 1/[\sigma^2(F_o^2) + (aP)^2 + (bP)]$, where $P = (F_o^2 + 2F_c^2)/3$.

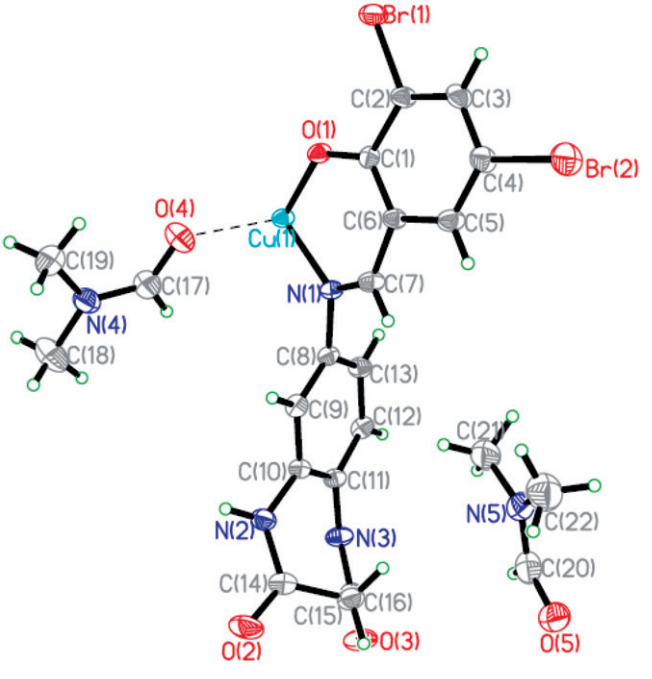


Figure 1. The crystal structure of **1**; hydrogens are shown as small circles with arbitrary radii (ellipsoids at 50% probability).

Table 2. Details of intermolecular hydrogen bonds in **1**.

Donor···H···Acceptor	[ARU]	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
N2···H2···O5[(a)]	$x, 1+y, z$	0.872	1.991	2.855	170.10
N3A···H3A···O4[(b)]	$x, -1+y, z$	0.943	1.964	2.890	166.98

Symmetry code: (a) $-x+1/2$, $y+1/2$, $-z+1/2$; (b) x, $y-1$, z.

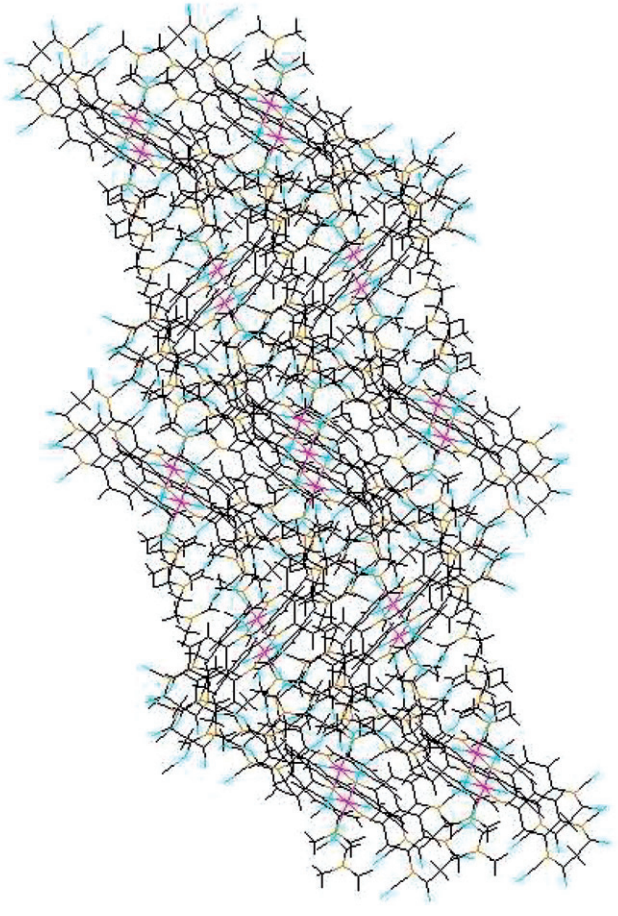


Figure 2. View of the 3-D structure of **1** along the *b*-axis.

completing a distorted octahedron as the overall geometry around Cu(II). The NH of amide forms hydrogen bonds with oxygens of DMF, either coordinated DMF (O4) or uncoordinated DMF (O5) (table 2). The overall crystal structure is chain type with DMF molecules from hydrogen bonds along *b*-axis (figure 2).

Interaction of **1** with CMP, CDP, CTP, dCMP, and dTMP was investigated through UV-Vis spectral titrations in DMSO/H_2O (9 : 1) by the addition of CMP, CDP, CTP, dCMP, and dTMP to the solution of **1**.

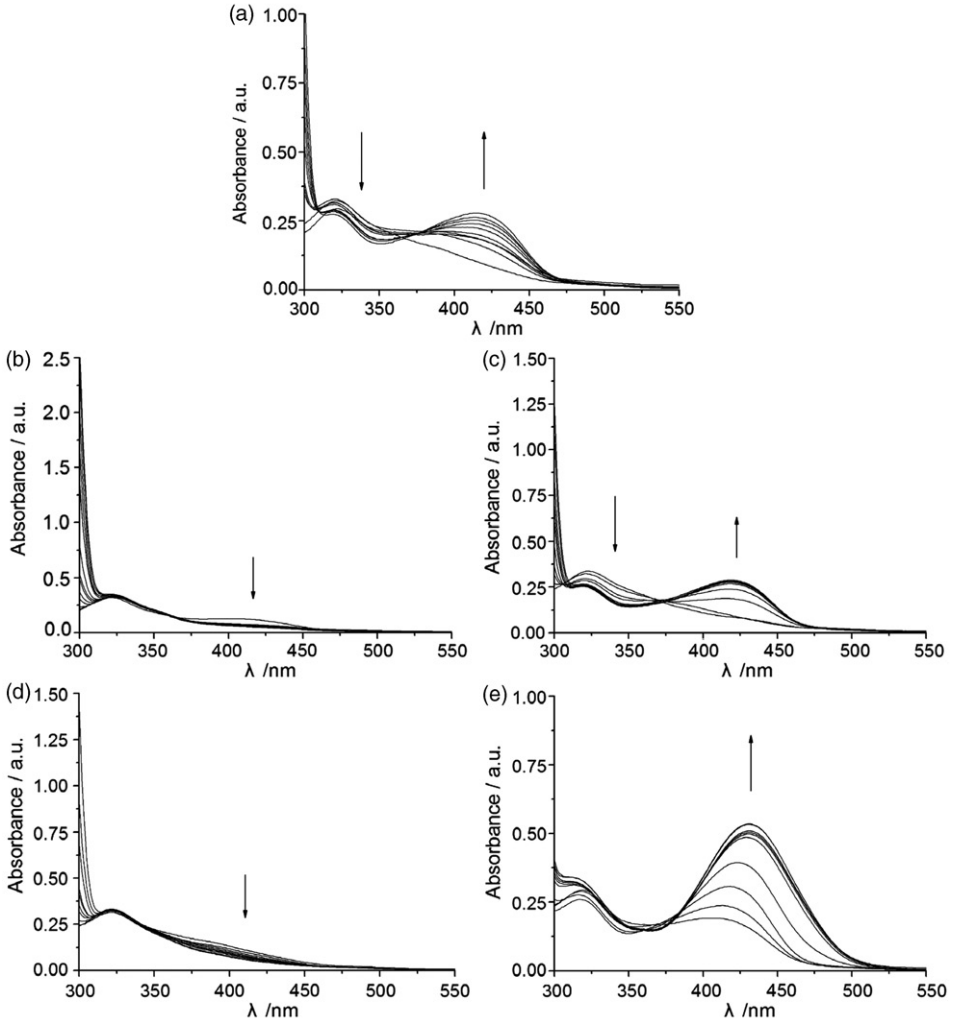


Figure 3. UV-Vis spectral changes of **1** (2.0×10^{-5} mol L^{-1}) upon the addition of CMP (a), CDP (b), CTP (c), dCMP (d), and dTMP (e); the concentration of nucleotides is from 0 to 160×10^{-5} mol L^{-1}. Arrows indicate the direction of increasing nucleotide concentration.

Figure 3 shows the interaction of **1** with nucleotides by absorption spectroscopy. With the addition of CMP, the absorbance band at 325 nm decreases gradually and the intensity of the band at 420 nm increases. One clear isosbestic point appears at 375 nm, showing that a stable complex is formed in solution with a certain stoichiometric ratio between **1** and CMP. Addition of CTP and dTMP also induces similar spectral change of **1**. The spectral change of **1** upon the addition of CDP is similar to that for addition of dCMP. The above results indicate that **1** shows different degrees of binding ability with various nucleotides.

In figure 4, Job's plot of **1** and CMP shows maximum at a molar fraction of 0.5, indicating that **1** binds CMP in a 1 : 1 ratio. Similar results can be obtained for other nucleotides (CDP, CTP, dCMP, and dTMP).

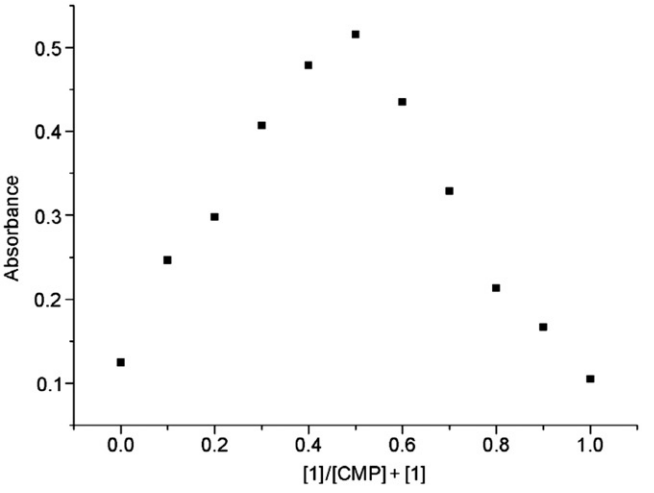


Figure 4. Job's plot for the complexation of **1** with CMP determined by UV-Vis.

Stability constants of **1** for nucleotides are calculated according to equation (1), the 1 : 1 host–guest complexation [29–32]:

$$X = X_0 + 0.5\Delta\varepsilon\{c_H + c_G + 1/K_s - [(c_H + c_G + 1/K_s)^2 - 4c_H c_G]^{1/2}\}, \quad (1)$$

where c_G and c_H are the concentrations of guest and host, respectively; X is the intensity of absorbance at certain concentrations of host and guest; X_0 is the intensity of the absorbance of host when the anion is not added; K_s is the affinity constant of host–guest complexation; and $\Delta\varepsilon$ is the change in molar extinction coefficient.

Curve fitting of the interaction between **1** and CMP, CDP, CTP, dCMP, and dTMP according to equation (1) is shown in figure 5. The high correlation indicates that receptor binds nucleotides in the ratio 1 : 1.

The stability constants of **1** with nucleotides were determined by non-linear least squares according to UV-Vis titration data (table 3). The binding ability of nucleotides with **1** is in the order: CDP > dCMP > CTP > CMP > dTMP, which is due to the moderate chain of CDP, which is a good fit for **1**. The binding ability of CDP with **1** is the strongest among the studied nucleotides. The stability constant for CDP is almost seven-fold greater than that for CTP and dCMP, and about 10-fold greater than that for CMP and dTMP. According to the crystal structure of **1**, nucleotides may interact by electrostatic interaction ($Cu^{2+}\cdots O^-$) for O^- from the phosphate of nucleotides. In addition, the cytidine of nucleotides forms π–π stacking with the seven-membered amide cycle of **1**. Therefore, the binding ability of nucleotides with **1** is influenced by the chain length of nucleotides. According to the stability constants, CDP stacks well with **1**. The binding ability of CDP with **1** is the highest among cytidine nucleotides and the interaction spectroscopy between CDP and **1** is different from other nucleotides.

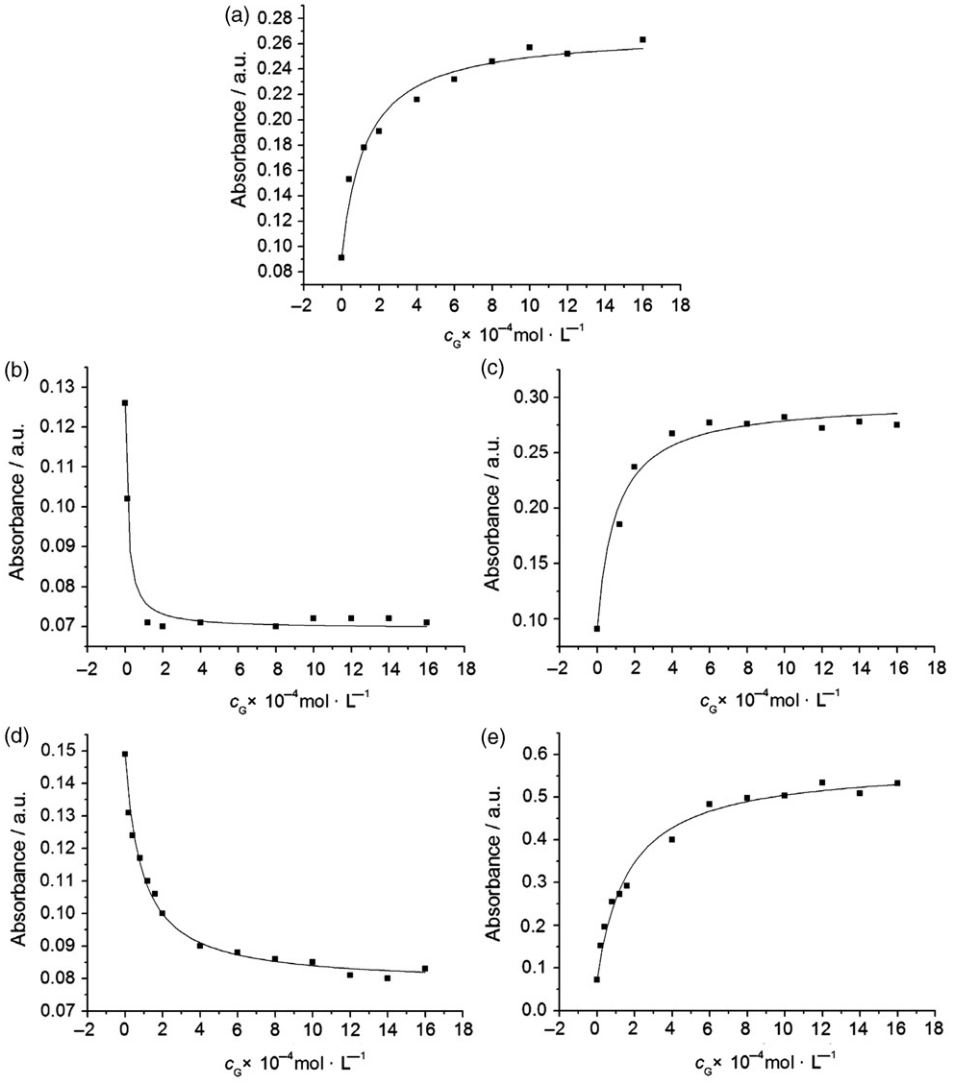


Figure 5. Curve fitting of the interaction between **1** and CMP (a), CDP (b), CTP (c), dCMP (d), and dTMP (e).

Table 3. Stability constants of **1** with nucleotides.

Nucleotides	K_s (mol L^{-1})
CMP	8000 ± 1000
CDP	$72{,}000 \pm 2000$
CTP	$10{,}000 \pm 2000$
dCMP	$11{,}300 \pm 900$
dTMP	6000 ± 700

4. Conclusion

We demonstrated a highly sensitive and selective absorption assay for CDP through **1** with a UV-Vis indicator. The uniqueness of this assay is that it successfully discriminates CDP from CMP, CTP, dCMP, and dTMP through visual change in absorption intensity, and **1** can be used as a supramolecular optic receptor for CDP. Studies are in progress to evaluate the selectivity of **1** toward other biologically important analytes.

Acknowledgment

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