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N-取代二吡啶甲基胺锌配合物的合成、与 DNA 作用和抗肿瘤活性

黄 娟 陈秋云* 王玲昀 付海舰 李 斌
(江苏大学化学化工学院,镇江 212013)

摘要:本文以 *N*-烯丙基二吡啶甲基胺(Aldpa)和 2,2-二(2-吡啶甲胺基)丙酸(Adpa)为配体,合成了 2 个锌配合物,并运用 IR,UV,ES-MS 等方法进行了表征。X-衍射晶体结构表明[(Adpa)Zn(CHCOO)]配合物中锌(Ⅱ)离子采取五配位三角双锥构型。紫外和荧光光谱滴定研究结果显示[(Adpa)Zn(CHCOO)]与 ctDNA 作用强于[(Aldpa)$ZnCl_2$]。用 MTT 法研究了配合物体外对肿瘤细胞生长的抑制作用。实验结果表明与 ctDNA 作用强的锌配合物抗肿瘤活性较好,二吡啶甲基胺氮原子上的取代基影响相应锌(Ⅱ)配合物的抗肿瘤活性。

关键词:DNA;抗肿瘤;锌配合物;光谱
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Synthesis, Interaction with DNA and Antitumor Activities of Zinc(Ⅱ) Complexes with *N*-substituted Di(picolyl)amines

HUANG Juan CHEN Qiu-Yun* WANG Ling-Yun FU Hai-Jian LI Bin
(*School of Chemistry and Chemical Engineering, Jiangsu University, Zhenjiang, Jiangsu* 212013)

Abstract: Two Zn(Ⅱ) complexes with Allyl bis(2-pyridylmethyl)amine (Aldpa), or bis(2-pyridylmethyl)amino-2-propionate(Adpa), were synthesized and characterized by IR, UV, ES-MS. The crystal structure shows that the Zn(Ⅱ) ion in [(Adpa)Zn(CHCOO)] is coordinated by three N atoms, one oxygen atom of the Adpa and one oxygen atom of CH_3COO^-, forming a distorted trigonal bipyramidal geometry. The spectrophotometric and fluorescence titration data indicate that the interaction between the [(Adpa)Zn(CHCOO)] with ct-DNA is more stronger than that of [(Aldpa)$ZnCl_2$]. The [(Adpa)Zn(CH_3COO)] is more active against the four cancer cells (Mcf-7, Eca-109, A549, Hela) than the [(Aldpa)ZnCl], indicating the antitumor activity of zinc(Ⅱ) complexes is dependent on its binding to DNA. The bioassay results also show that the substituents introduced on the secondary amino nitrogen atom of dpa have great contribution to the antitumor activities of these zinc(Ⅱ) complexes. Information obtained from the present is helpful to development of therapeutic agents. CCDC: 709681.

Key words: DNA; anticancer activity; zinc(Ⅱ) complex; spectroscopy

Di(picolyl)amine (dpa) and its derivatives are used as neutral, nondeprotonated chelating ligands to complex Cu(Ⅱ), Zn(Ⅱ), Fe (Ⅱ, Ⅲ) ions to mimic non-heme dioxygenase or to synthesis metal complexes with open coordination sites[1~4]. Zn(Ⅱ)-dpa complexes were employed as binding sites for histidine residues to study metalloenzyme function in bioinorganic chemistry, or to direct supramolecular self-assembly[5~7]. The utility of dpa is enhanced by the ease with which substituents may be introduced on the amino nitrogen atom, thus

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*通讯联系人。E-mail:chenqy@ujs.edu.cn
第一作者:黄 娟,女,26 岁,硕士研究生;研究方向:无机药物化学。

allowing the controlled modification of solubility and molecular conformation through the non-bonding interactions[8,9]. For example, the *N*-substituted di(picolyl) amines is more active against the proliferation of cancer cells than dpa[10]. The mononuclear copper(Ⅱ) complex of 1-(bis-pyridin-2-ylmethyl-amino)-3-chloropropane-2-ol) was reported to promote cell death of THP-1 carcinogeni cells by apoptosis[11]. Zn(Ⅱ) complexes of 1-[3-(2-pyridyl) pyrazol-1-ylmethyl]naphthalene were found active against the proliferation of cancer cells[12]. So study on the zinc(Ⅱ) complexes of *N*-substituted Di(picolyl)amines is important to find new types of antitumor complexes. DNA is the primary target molecule for most anticancer complexes. Thus, investigations on the interactions of DNA with metal complexes are meaningful to design new types of pharmaceutical molecules[13]. Here, we report the synthesis, characterization, interaction with DNA and antitumor activities of Zn(Ⅱ) complexes with *N*-allyl bis (2-pyridylmethyl)amine (Aldpa) and bis(2-pyridylmethyl)amino-2-propionate (Adpa).

1 Experimental section

1.1 Materials and instruments

All chemicals used in the syntheses were of reagent grade and were used without further purification. Calf thymus DNA (ct-DNA), Tris (hydroxymethyl) aminomethane) (tris), and ethidium bromide (EB) and di (picolyl)amine (dpa) were purchased from Sigma-Aldrich. *N*-allyl bis(2-pyridylmethyl)amine (Aldpa) and bis (2-pyridylmethyl)amino-2-propionate (Adpa) were synthesized as reported[14]. Water was purified with a Millipore Milli-Q system. The C, H and N microanalyses were performed on Vario EL elemental analyzer. The Metal ions were determined by Vista ICP-OES. The molar electrical conductivities in DMF solution containing 10^{-4} mol·L^{-1} complex were measured at 250.1 ℃ using a BSA-A conductometer. The electronic absorption spectra were recorded in the 900-190 nm region using the VARIAN CARY 50-BIO UV-VIS spectrophotometer. Infrared spectrum was recorded on a Nicolet-470 spectrophotometer. The electrospray mass spectra (ES-MS) were determined on a Finnigan LCQ mass spectrograph and the concentration of the samples was about 1.0 μmol·L^{-1}. The fluorescence spectra were measured with Fp-750w Fluorometer. DNA bind experiment was performed as reported[14].

1.2 Preparation of [(Aldpa)ZnCl$_2$] (1)

To a stirred ethanol solution (5 cm^3) of N-Allyl bis (2-pyridylmethyl)amine (Aldpa) (119.7 mg, 0.5 mmol), a solution of $ZnCl_2$ (68.1 mg, 0.5 mmol) in ethanol (10 cm^3) was added dropwise. The mixture was heated at 70 ℃ for 2h and then cooled to room temperature. The solution was filtered and the filtrate was evaporated by a rotary evaporator under reduced pressure at 50℃. The white products [(Aldpa)$ZnCl_2$] was obtained. Yield, 64%. Anal. Calc. for or $C_{15}H_{17}Cl_2ZnN_3$(%): C, 47.96; H, 4.56; N, 11.19, Zn, 17.41; Found(%): C, 47.33; H, 4.91; N, 10.82, Zn, 17.56. IR (cm^{-1}): 3 074s ν(=CH); 2 918m ν(-CH_2-); 1 634m, 1 602s, 1 571m ν(C=C, C=N); 774s δ (CH, pyridine); 406m ν(Zn-N). UV-Vis (λ_{max}/nm, H_2O): 194.0 (39 100 L·mol^{-1}·cm^{-1}), 260 (22 600 L·mol^{-1}·cm^{-1}). Λ_m (CH_3OH): 16.9 S·cm^2·mol^{-1}.

1.3 Preparation of [(Adpa)Zn(CH_3COO)] (2)

To a stirred ethanol solution (5 mL) of Ethyl 2-[bis (2-pyridylmethyl)amino] propionate (Adpa) (142.2 mg, 0.48 mmol), the pH of the solution was adjusted to ca. 9 with NaOH, a solution of $Zn(CH_3COO)_2·2H_2O$ (105.6 mg, 0.48 mmol) in ethanol (7 mL) was added dropwise. Then the reaction solution was refluxed for 2 h and cooled to room temperature. The resulting solution was filtered and subsequently kept the filtrate aside for slow evaporation. The colorless crystals suitable for X-ray diffraction were obtained after a few days. Yield, 74%. Anal. Calcd. for $C_{17}H_{19}N_3O_4Zn$ (%): C, 51.73; H, 4.85; N, 10.64; Zn, 16.57; Found(%): C, 51.78; H, 4.92; N, 10.72; Zn, 16.67. IR (cm^{-1}): 3 074s ν (=CH); 2 967m ν(-CH_2-); 1 641s, 1 388m ν(C=O); 1 608s, 1 571m ν(C=C, C=N); 778s δ (CH, pyridine); 406m ν (Zn-N). UV-Vis (λ_{max}/nm, H_2O): 194.0 (39 900 L·mol^{-1}·cm^{-1}), 261 (23 400 L·mol^{-1}·cm^{-1}). Λ_m (CH_3OH): 20.6 S·cm^2·mol^{-1}.

1.4 Crystal structure determination

The X-ray diffraction data (Table 1) was collected at 293(2) K on CrystalClear CCD Area Detector with Mo $K\alpha$ monochromatic radiation (λ=0.071 073 nm). A total of 16 643 reflections were collected in range of 2.80°<θ<27.48°, of which 3 850 (R_{int}=0.038 2) were

Table 1　Crystal data and structure refinement details for the complex [(Adpa)Zn(CH_3COO)]

Empirical formula	$C_{17}H_{19}N_3O_4Zn$	D_c / (g·cm^{-3})	1.489
Formular weight	394.72	Absorption coefficient / mm^{-1}	1 632
Color / shape	Colorless / block	θ range / (°)	2.80~27.48
Crystal system	Monoclinic	Index ranges	$-40 \leqslant h \leqslant 40, -9 \leqslant k \leqslant 9, -23 \leqslant l \leqslant 23$
Space group	*C*2/*c*	Reflection collected	16643
Temperature / K	293(2)	Independent reflections (R_{int})	3 850 (0.032 8)
a / nm	3.1(2)	Observed reflns [$I>2\sigma(I)$]	3 447
b / nm	0.725 4(4)	Absorption correction	Empirical
c / nm	1.795 4(12)	No. restrains	0
β / (°)	123.651(6)	No. parameters	228
V / nm^3	3.362(4)	Goodness-of-fit on F^2	1.115
Z	8	Final *R* indices [$I>2\sigma(I)$]	R_1=0.038 2, wR_2=0.091 4
Crystal size / mm	0.5×0.5×0.3	*R* indices (all data)	R_1=0.044 0, wR_2=0.094 5
F(000)	1.560		

independent, and 3 447 with $I>2\sigma(I)$ were considered as observed. The structure was solved using direct methods and difference Fourier synthesis with SHELXS -97 program, and the non-hydrogen atoms were refined anisotropically with SHELXL-97 using full-matrix least-squares procedures based on F^2 values[15,16]. The hydrogen atom positions were fixed geometrically at calculated distances and allowed to ride on the parent atoms. All calculations were performed using the SHELX-97 programs.

CCDC: 709681.

1.5　Cytotoxicity testing

The cytotoxicity assay was in four kinds of cells line (human breast carcinoma cells Mcf-7, human esophageal cancer cells Eca-109, human cervical cancer Hela cells and human lung adenocarcinoma A549 cells). Cells were cultured in RMPI 1640 medium containing 4.8 g·L^{-1} of Hepes, 2.2 g·L^{-1} $NaHCO_3$ and supplemented with penicillin/streptomycin(1 000 units·mL^{-1}), and 10% calf serum. Hela, Mcf-7 cells were cultured in DMEM medium containing 10% fetal bovine serum. All cells were grown at 37 ℃ in a humidified atmosphere in the presence of 5% CO_2. Eca-109, A549 , Mcf-7, Hela cells were seeded at a density of 4×10^4 cells·mL^{-1} into sterile 96 well plates and grown in 5% CO_2 at 37 ℃. Test compounds were dissolved in H_2O and diluted with culture media. After 24 hour, compounds were added, treated for 48 hours. Cell viability was determined by the 3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenpyltetra-zolium bromide (MTT) assay by measuring the absorbance at 570 nm with ELISA reader. IC_{50} was calculated by the software provided by Nanjing university. Each test was performed in triplicate.

2　Results and discussion

2.1　Characterization of the complexes 1 and 2

The structures of the complexes **1** and **2** were characterized by elemental analyses, molar conductivities, IR, UV spectra and ES-MS. The elemental analyses agree well with the proposed structures of the complexes. The molar conductances of the two complexes in methanol reveal the non-electrolyte nature of the two complexes[17]. The IR spectra show that two pyridyl ring vibration bands at approximately 1 590 and δ(CH) vibration of pyridyl ring at approximately 760 cm^{-1} were shifted to 1 602~1 607 cm^{-1} and 774~778 cm^{-1} for complexes **1** and **2**. These shifts suggest that the nitrogen atoms of pyridyl ring of the ligands donate a pair of electrons each to the central metal forming coordinate covalent bond[18, 19]. The weak bands at 445~447 cm^{-1} show the existence of Zn-N bond. The infrared spectra of the complexe **2** show ν_{as}(COO) stretching frequencies at 1 644 cm^{-1} and ν_{sym}(COO) at 1 389 cm^{-1}. The difference between ν_{as}(COO) and ν_{sym}(COO) are about 205 cm^{-1}, suggesting that the carboxylate groups

coordinate to the metal atoms only as monodentate ligands.

The ES-MS data and their assignments for the two complexes in methanol were shown in Table 2. The peaks at *m/z*=178.92 (100) and 382.92(100) for the two complexes correspond to the species {[(Aldpa)Zn+$2H_2O$]$_2CH_3OH$}$^{2+}$ (**1**) and {[(Adpa)Zn+CH_3OH]$_2CH_3OH$}$^+$ (**2**), respectively, which were formed by losing the coordinated Cl anions (or CH_3COO^-) and binding different number of solvent molecules. It was reported that metal complexes with open coordination sites, such as dpa-M(Ⅱ) (M = Zn(Ⅱ), Cu(Ⅱ), Ni(Ⅱ), Fe(Ⅱ, Ⅲ)), were used in molecular recognition [8,9]. The ES-MS results show the coordinated Cl^- or the CH_3COO^- in complexes **1** and **2** were easily lost or replaced by solvents. So we deduced that the complexes **1** and **2** were similar to those complexes with open coordination sites.

Table 2 Mass Spectrum of [(Aldpa)ZnCl$_2$] and [(Adpa)Zn(CH$_3$COO)] in methanol solution

Complexes	Mass No.	Fragments	Relative abundance / %
[(Aldpa)ZnCl$_2$] (**1**)	240.25	[(Aldpa)+H$^+$]$^+$	35
	262.17	{[(Aldpa)Zn]$_2^{4+}$+CH_3O^-+4CH_3OH+H_2O}$^{3+}$	25
	194.75	{[(Aldpa)Zn+CH_3OH+2H_2O]$_2CH_3OH$}$^{2+}$	57
	178.92	{[(Aldpa)Zn+2H_2O]$_2CH_3OH$}$^{2+}$	100
[(Adpa)Zn(CH$_3$COO)] (**2**)	382.92	{[(Adpa)Zn+CH_3OH]$_2CH_3OH$}$^+$	100
	203.08	{[(Adpa)Zn+H$^+$+2H_2O+CH_3OH}$^{2+}$	35
	423.00	{[(Adpa)Zn+4H_2O]$_2CH_3OH$}$^+$	22
	308.17	[Adpa+2H$^+$+2H_2O]$^+$	14

2.2 Crystal Structure of [(Adpa)Zn(CH$_3$COO)] (2)

The crystal structure of [(Adpa)Zn(CH$_3$COO)] (**2**) with the atomic labeling scheme is shown in Fig.1 and the selected bond lengths and angles are listed in Table 3. The monodepronated ligand (Adpa) acts as a tetradentate ligand toward a zinc(Ⅱ) ion. The zinc(Ⅱ) is coordinated by three N atoms (N(1), N(2), N(3), one oxygen atom (O(1)) of the (Adpa) and the oxygen atom (O(3)) of CH_3COO^- anion, resulting a five coordinated mononuclear zinc(Ⅱ) complex. The five coordinated zinc(Ⅱ) complex [(Adpa)Zn(CH$_3$COO)] forms a distorted trigonal bipyramidal coordination geometry, similar to that of reported copper(Ⅱ) complex [Cu(tmpa)(Cl)](BPh$_4$) (tmpa=tris(2-pyridylmethyl) amine)[20]. The O(1), N(3), and O(3) form the equatorial trigonal plane, while the N(1) and N(2) occupy the apical positions. The zinc(Ⅱ) ion is shifted by 0.010 02 nm out of the equatorial plane towards the N(2) atom. The bond distances of Zn(1)-

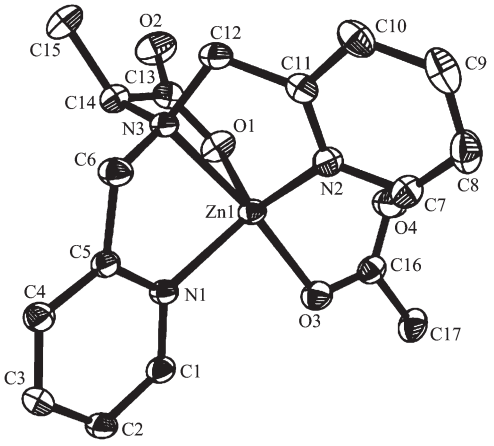


Fig.1 Crystal structure for the complex [(Adpa)Zn(CH$_3$COO)] (**2**), hydrogen atoms are omitted for clarity, Thermal ellipsoids are drawn at 50% probability

Table 3 Selected bond lengths (nm) and bond angles (°) for the complex [(Adpa)Zn(CH$_3$COO)]

Zn(1)-O(1)	0.197 9(2)	Zn(1)-N(2)	0.209 1(2)	Zn(1)-N(3)	0.227 9(2)
Zn(1)-O(3)	0.199 5(2)	Zn(1)-N(1)	0.209 9(2)		
O(1)-Zn(1)-O(3)	108.02(9)	O(3)-Zn(1)-N(2)	103.75(8)	N(2)-Zn(1)-N(1)	111.29(9)
O(1)-Zn(1)-N(3)	78.98(9)	O(3)-Zn(1)-N(1)	94.21(8)	N(1)-Zn(1)-N(3)	77.32(7)
O(1)-Zn(1)-N(2)	119.83(8)	O(3)-Zn(1)-N(1)	170.92(7)		
O(1)-Zn(1)-N(1)	115.63(9)	N(2)-Zn(1)-N(3)	76.78(7)		

N(1) and Zn(1)-N(2) are 0.209 9(2) nm and 0.209 1(2) nm. The N(2)-Zn(1)-N(1) angle is 111.29°.

2.3 Binding characteristics of complexes with DNA

It is observed that the absorption bands of [(Aldpa)$ZnCl_2$] (**1**) and [(Adpa)Zn(CH_3COO)] (**2**) at 203 nm exhibited hypochromism of 35.84% and 40.63%, respectively, and bathochromism shift of about 6nm when the addition of ct-DNA to the solution of the complexes. The spectrophotometric titration of the complex **2** is shown in Fig.2. The hypochromism was caused possibly by the intercalation binding mode between the complexes and ct-DNA. Bathochromism shift indicates the π^* orbital of intercalated ligand couple with the π orbital of the base pairs, thus reducing the π-π^* transition energy [21]. These results suggest an association existence between the two complexes with ct-DNA. So we primarily speculate that the two complexes interacting with ct-DNA have the same mode of electrostatic effect or intercalation.

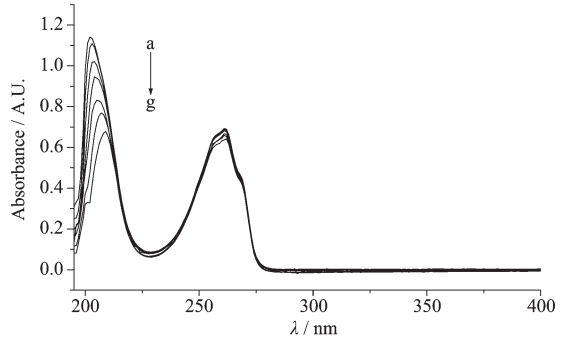
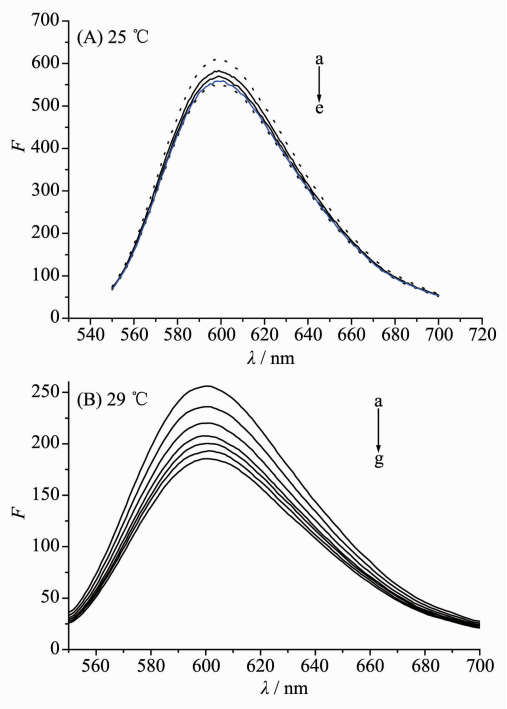


Fig.2　Electronic spectra of [(Adpa)Zn(CH_3COO)] (**2**) (100 μmol·L^{-1}) in the presence of increasing amounts of ct-DNA; DNA concentrations are 0, 42.7, 85.5, 128.2, 171.0, 213.7 and 256.5 μmol·L^{-1} for spectra (a~g), respectively

The binding for the complexes to calf thymus DNA was also studied by the fluorescence method. When [(Aldpa)$ZnCl_2$] (**1**) and [(Adpa)Zn(CH_3COO)] (**2**) were added into the solution of DNA-EB complex, respectively, the fluorescence intensity of DNA-EB complex decreases with the increasing concentration (Fig.3(A, B)). According to linear Stern-Volmer equation, the K_q values for the complex **1** is 3.17×10^{11} L·s^{-1}·mol^{-1} at 25 ℃, and for the complex **2** is 5.79×10^{12} L·s^{-1}·mol^{-1} at 25 ℃, which are far greater than 2.0×10^{10} L·s^{-1}·mol^{-1} [22]. This suggests that the binding for the two complexes with DNA are a static quenching process, which is well consistent with the results of spectrofluorimetric titration. According to the K_q values, it can be concluded that the binding force between [(Adpa)Zn(CH_3COO)] and DNA is stronger than that of [(Aldpa)$ZnCl_2$].



(A): Total concentrations of [(Aldpa)$ZnCl_2$] are (a) 0, (b) 50.0, (c) 100, (d) 150, (e) 200 μmol·L^{-1}, EB and DNA concentration are 2 and 50 μmol L^{-1}; (B): Total concentrations of [(Adpa)Zn(CH_3COO)] are (a) 0, (b) 10.0, (c) 20.0, (d) 30.0, (e) 40.0, (f) 50.0, (g) 60 μmol·L^{-1}, EB and DNA concentration are 0.68 and 20 μmol·L^{-1}

Fig.3　Fluorescence spectra of DNA-EB in the presence of [(Aldpa)$ZnCl_2$] (A) and [(Adpa)Zn(CH_3COO)] (B) at 25 ℃

The binding constants of the complexes **1** and **2** with DNA in the presence of EB are determined using the following relationship[23].

$$\lg[(F_0-F)/F]=n\lg K_A+n\lg[c_{D_t}-nc_{N_t}(F_0-F)/F_0] \qquad (1)$$

where c_{N_t} and c_{D_t} are the total concentration of DNA-EB complex and complex, respectively.

On the assumption that n in the bracket is equal to 1, the curve $\lg[(F_0-F)/F]$ versus $\lg[c_{D_t}-nc_{N_t}(F_0-F)/F_0]$ is drawn and fitted linearly, then the slope n can be obtained. If the slope n obtained is not equal to 1, then it is substituted into the bracket and the curve $\lg[(F_0-F)$

/*F*] versus lg[$c_{D_t}-nc_{N_t}(F_0-F)/F_0$] is drawn again. Such the above process is repeated again and again till the only one value of *n* is got. Based on the intercept and *n*, K_A can be obtained. The plots of lg[$(F_0-F)/F$] versus lg[$c_{D_t}-nc_{N_t}(F_0-F)/F_0$] for DNA-EB complex in the presence of complex are shown in Fig.4 at various temperatures.

The binding constants are listed in Table 4. The binding constant of complex **2** at 25 ℃ is 1.21×10^3 L·mol^{-1}, which is far larger than that (4.52 L·mol^{-1}) of complex **1**. The binding constants of the two complexes increase with the temperature (Table 4). This suggests that the binding reaction of the complexes **1** and **2** with DNA is endothermic, and increasing temperature benefits their binding with DNA. This point is further proved by the value of ΔH, the enthalpy change of the binding reactions. The thermodynamic parameters were calculated by the equations as follows.

$$\ln(K_{A2}/K_{A1})=(1/T_1-1/T_2)\Delta H/R \quad (2)$$

$$\Delta G=\Delta H-T\Delta S=-RT\ln K_A \quad (3)$$

where ΔG, ΔS are the free energy change and the entropy change, respectively. Based on the binding constants at various temperature, the values of ΔH, ΔG and ΔS calculated are listed in Table 5. Because $\Delta S>0$, the DNA-[(Aldpa)$ZnCl_2$] and DNA-[(Adpa)Zn(CH_3COO)] association are based upon the entropically driven hydrophobic effect[24].

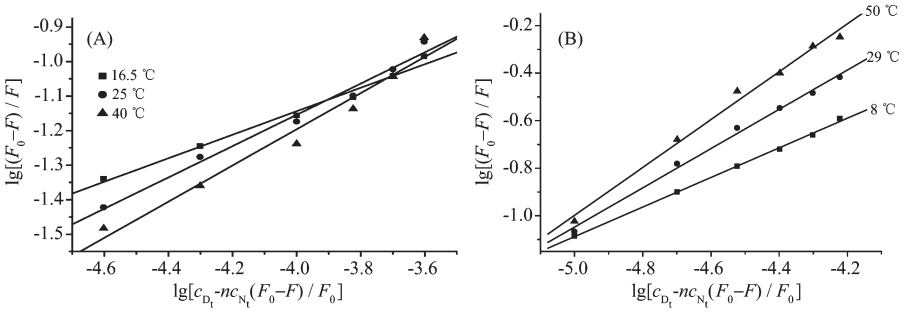


Fig.4 Plots of lg[$(F_0-F)/F$] vs lg[$c_{D_t}-nc_{N_t}(F_0-F)/F_0$] for [(Aldpa)$ZnCl_2$] (A) and [(Adpa)Zn($CH_3COO$)] (B) at various temperatures

Table 4 Binding constant (K_A) and binding site (*n*) of [(Aldpa)$ZnCl_2$] and [(Adpa)Zn(CH_3COO)] with DNA at various temperatures

Complexes	Temperature / ℃	K_A / (L·mol^{-1})	*n*
[(Aldpa)$ZnCl_2$]	16.5	1.65	0.34
	25	4.52	0.45
	40	7.91	0.52
[(Adpa)Zn(CH_3COO)]	8	106.33	0.62
	25	1.21×10^3	0.83
	50	1.1×10^4	1.00

Table 5 Thermodynamic parameters of the binding reaction of [(Aldpa)$ZnCl_2$] and [(Adpa)Zn(CH_3COO)] with DNA

Complexes	Temperature / ℃	ΔH / (kJ·mol^{-1})	ΔG / (kJ·mol^{-1})	ΔS / (J·mol^{-1}·K^{-1})
[(Aldpa)$ZnCl_2$]	16.5~25	85.43	−3.74	299.09
	16.5~40	50.39	−5.39	178.11
[(Adpa)Zn(CH_3COO)]	8~25	81.79	−10.91	329.70
	8~50	83.39	−11.31	335.4

2.4 Inhibition on the proliferation of cancer cells

Complexes **1** and **2** were studied for their antitumor activity in vitro by determining the inhibitory percentage against growth of cancer cells Mcf-7, A549, Hela, and Eca-109 using the method of 3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenpyltetrazolium bromide reduction (MTT method). The IC_{50} data of the two complexes and the ligands (Aldpa and Adpa) were shown in Table 6. The complex **2** can inhibit the proliferation of the Mcf-7 cell with IC_{50} in the range of 0.69 μmol·L^{-1},

Table 6　Inhibition on the proliferation of human cancer cells for Zinc(Ⅱ) complexes

Tested complex	$IC^*_{50\text{-}Mcf\text{-}7}$ / (μmol·L^{-1})±SD	$IC^*_{50\text{-}HeLa}$ / (μmol·L^{-1})±SD	$IC^*_{50\text{-}A549}$ / (μmol·L^{-1})±SD	$IC^*_{50\text{-}Eca109}$ / (μmol·L^{-1})±SD
[(Aldpa)$ZnCl_2$] (**1**)	87.12±0.02	95.46±0.02	97.08±0.02	78.45±0.02
[(Adpa)Zn(CH_3COO)] (**2**)	0.69±0.02	4.82±0.02	4.54±0.02	1.51±0.02
Aldpa	31.14±0.02	22.14±0.02	28.36±0.02	18.41±0.02
Adpa	3.12±0.02	7.12±0.02	25.24±0.02	6.65±0.02

*IC_{50} was average data of triplicate assay.

which is smaller than that (87.12 μmol·L^{-1}) of complex **1**. These were possibly due to the solubility; molecular conformation and the DNA intercalation of complexes **2** are different from that of the complex **1**. These data indicate that the substituents introduced on the secondary amino nitrogen atom of dpa have great contribution to the antitumor activities of these zinc(Ⅱ) complexes. It is also found that the Aldpa was more active against the proliferation of the four cancer cells than the complex **1**, indicating the coordination of zinc (Ⅱ) with Aldpa can decrease the toxicity of Aldpa.

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