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Spectroscopic and molecular modeling methods to study the interaction between naphthalimide-polyamine conjugates and DNA

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ABSTRACT

The effect of polyamine side chains on the interaction between naphthalimide-polyamine conjugates (**1–7**) and herring sperm DNA was studied by UV/vis absorption and fluorescent spectra under physiological conditions (pH = 7.4). The diverse spectral data and further molecular docking simulation *in silico* indicated that the aromatic moiety of these compounds could intercalate into the DNA base pairs while the polyamine motif might simultaneously locate in the minor groove. The triamine compound **7** can interact more potently with DNA than the corresponding diamine compounds (**1–6**). The presence of the bulky terminal group in the diamine side chain reduced the binding strength of compound **1** with DNA, compared to other diamine compounds (**2–6**). In addition, the increasing methylene number in the diamine backbone generally results in the elevated binding constant of compounds–DNA complex. The fluorescent tests at different temperature revealed that the quenching mechanism was a static type. The binding constant and thermodynamic parameter showed that the binding strength and the type of interaction force, associated with the side chains, were mainly hydrogen bonding and hydrophobic force. And the calculated free binding energies of molecular docking are generally consistent with the stability of polyamine–DNA complexes. The circular dichroism assay about the impact of compounds **1–7** on DNA conformation testified the B to A-like conformational change.

1. Introduction

The study on the interaction between small molecules and DNA has been caught people's attention of recent research in the scope of life science, chemistry and clinical medicine [1–3]. As we now know, DNA is the carrier of genetic information and gene expression of the material basis, which plays an extremely important role in the process of human life for its abilities to interfere with transcription (gene expression and protein synthesis) and DNA replication, a major step in cell growth and division. Generally speaking, a variety of small molecules usually interacts reversibly with DNA in three primary ways: (1) intercalation of planar or approximately planar aromatic ring systems between base-pairs [4]; (2) groove binding in which the small molecules bound on nucleic acids are located in the major or minor groove [4]; (3) binding along the exterior of DNA helix that is through interactions which are generally nonspecific and are primarily electrostatic [5–8].

The 1, 8-naphthalimide derivatives are the DNA intercalating agents because of their consisting of a flat, generally p-π deficient aromatic system of which binds to DNA by insertion between the base pairs of the double helix [4]. They displayed good antitumor activity due to their intercalation causing the base pairs to separate vertically, so twisting the sugar phosphate backbone and changing the degree of rotation between successive base pairs [9–17]. Polyamines can bind to DNA by hydrogen bond or electrostatic interactions and cause DNA conformational changes [18–21]. Naphthalimide-polyamine conjugates have been also proved to display good activity *in vitro* and intercalate into the DNA [22–26]. They could induce DNA conformational transition and the substituted groups linked to naphthalimide scaffold displayed some impacts on related interaction [26]. It is ever reported that naphthalimide-polyamine conjugates aren't surely the DNA intercalators [27]. However, to date the side chain effects on the interactions between different naphthalimide-polyamine conjugates and DNA, including numbers of free nitrogen atoms, type of terminal amino group and numbers with position of methylene, have been reported rarely. Besides, types of DNA conformational transition and the interaction mode need to be clarified. The present work will address these issues by the interaction between naphthalimide-polyamine conjugates (**1–7**, Fig. 1) and herring sperm DNA.

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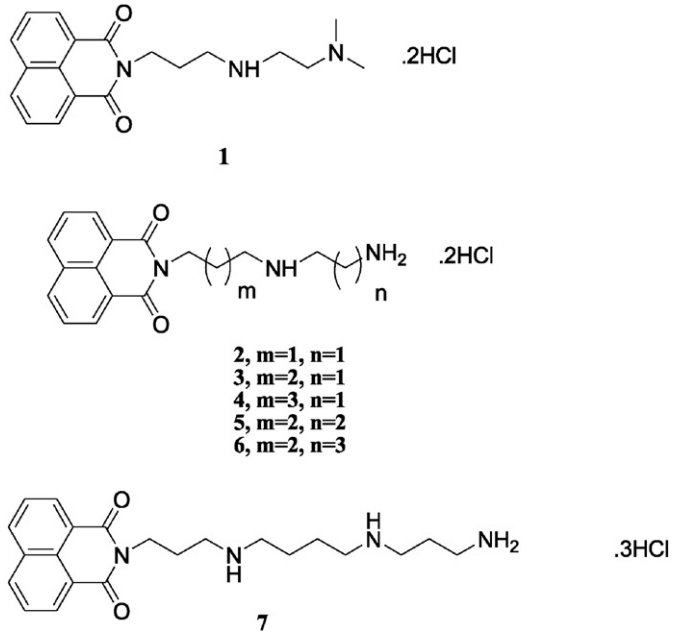

Fig. 1. Structures of naphthalimide-polyamine conjugates.

2. Materials and Methods

2.1. Apparatus

UV–vis absorption spectra were measured on a Unicam UV 500 spectrophotometer using a 1.0 cm cell. Fluorescence measurements were performed with a Cary Eclipse spectrofluorimeter. Circular dichroism spectrum measurements were performed on a Modle 420 SF (USA) automatic recording spectrophotometer in a 1 mm quartz cell.

2.2. Materials

Naphthalimide-polyamine conjugates **1–7** were prepared previously [22–25]. Their solutions (2.00×10^{-4} mol·L^{-1}) were either prepared with the Tris–HCl (pH = 7.4) buffer solution (UV and Fluorescence) or the phosphate buffer saline (PBS, pH = 7.4) buffer solution (CD) and stored at 4 °C. Herring sperm DNA (Sino-American Biotechnology Company, Beijing, China) was used without further purification. And its stock solution was prepared either by dissolving an appropriate amount of DNA in Tris–HCl (pH = 7.4) buffer solution (2.284×10^{-4} mol·L^{-1}, for UV and Fluorescence) or PBS (pH = 7.4) buffer solution (4.568×10^{-4} mol·L^{-1}, for CD), stored at 4 °C. Ethidium bromide (EB, Sigma Chem. Co., USA) stock solution (1.57×10^{-5} mol·L^{-1}) was prepared by dissolving its crystals with the Tris–HCl buffer solution and stored in a cool and dark place.

2.3. Procedures

2.3.1. UV–Vis Measurement

2 mL solution of compounds **1–7** (2.00×10^{-4} mol·L^{-1} in Tris–HCl (pH = 7.4) was mixed with 0.0, 0.10, 0.20, 0.30, 0.60, 0.90 1.20, 1.50, 1.80, 2.10, 2.40, 2.70 and 3.0 mL of herring sperm DNA (2.284×10^{-4} mol·L^{-1}) respectively. The mixture was diluted to 5 mL with Tris–HCl (pH = 7.4). Thus, two groups of samples were prepared in the concentration of DNA at 0.0, 4.56, 9.13, 13.69, 27.4, 41.08, 54.77, 68.46, 82.15, 95.84, 109.54, 123.23 and 136.92×10^{-6} mol·L^{-1}. One contained only compounds **1–7** (80×10^{-6} mol·L^{-1}) as control, the others contained different concentration of DNA but had the same concentration of compounds **1–7**. All the above solutions were shaken for 30 min at room temperature.

2.3.2. Fluorescence Measurement

*2.3.2.1. Interaction of Compounds **1–7** with DNA.* Preparation of samples is the same as that of UV–Vis samples. Fluorescence wavelengths and intensity areas of samples **1–7** were measured at 298, 303 and 310 K in the wavelength range of 355–690 nm with exciting wavelength at 345 nm.

*2.3.2.2. Interaction of Compounds **1–7** With DNA-EB Complex.* 0.3 mL solution of herring sperm DNA (2.284×10^{-5} mol·L^{-1} in Tris–HCl (pH = 7.4) and 0.4 mL EB (1.57×10^{-5} mol·L^{-1}) were mixed with 0.0, 0.10, 0.20, 0.30, 0.60, 0.90 1.20, 1.50, 1.80, 2.10, 2.40, 2.70 and 3.00 mL of compounds **1–7** (2.0×10^{-4} mol·L^{-1}) respectively. The mixture was also diluted to 5 mL with Tris–HCl (pH = 7.4). Thus, three groups of samples were prepared in the concentration of compounds **1–7** at 0.0, 4.0, 8.0, 12.0, 24.0, 36.0, 48.0, 60.0, 72.0, 84.0, 96.0 and 108.0 and 120.0×10^{-6} mol·L^{-1}. One contained only DNA (13.7×10^{-6} mol·L^{-1}) and EB (15.7×10^{-6} mol·L^{-1}) as control, the others contained different concentration of compounds **1–7** but had the same concentration of DNA and EB. All the above solution was shaken for 30 min at room temperature. Fluorescence wavelengths and intensity areas of samples **1–7** were measured at 298, 303 and 310 K in the wavelength range of 520–800 nm with exciting wavelength at 510 nm.

2.3.2.3. Iodide Quenching. 0.5 mL solution of compounds **1–7** (2.00×10^{-4} mol/L) and 0.5 mL herring sperm DNA (22.84×10^{-4} mol/L) in Tris–HCl (pH = 7.4) were mixed with 0.0, 0.20, 0.40, 0.60, 0.80, 1.00 1.20, 1.40, 1.60, 1.80, and 2.00 mL of KI (2.0×10^{-2} mol·L^{-1}) respectively. Meanwhile, 0.5 mL solution of compounds **1–7** (2.00×10^{-4} mol/L) was only mixed with 0.0, 0.20, 0.40, 0.60, 0.80, 1.00 1.20, 1.40, 1.60, 1.80, and 2.00 mL of KI (2.0×10^{-2} mol·L^{-1}) respectively. The two kinds of mixtures were diluted to 5 mL with Tris–HCl (pH = 7.4) to possess the concentration of KI at 0.0, 400, 800, 1200, 2400, 3600, 4800, 6000, 7200, 8400, 9600, 10,800, 12,000 $\times 10^{-6}$ mol·L^{-1}. The control groups contained only compounds **1–7** (20×10^{-6} mol·L^{-1}) and different concentration of KI, the other samples contained different concentration of KI and fixed concentrations of compounds **1–7** (20×10^{-6} mol·L^{-1}) and DNA (22.82×10^{-6} mol·L^{-1}). All the above solution was shaken for 30 min at room temperature. Fluorescence wavelengths and intensity areas of samples were the same as Section 2.3.2.1.

*2.3.2.4. Effect of Ionic Intensity on the Interaction Between Compounds **1–7** and DNA.* 1.0 mL solution of compounds **1–7** (2.00×10^{-4} mol·L^{-1}) and herring sperm DNA 1.0 mL (2.284×10^{-4} mol·L^{-1}) in Tris–HCl (pH = 7.4) were mixed with 0.0, 0.10, 0.20, 0.30, 0.60, 0.90 1.20, 1.50, 1.80, 2.10, 2.40, 2.70 and 3.00 mL of NaCl (4.0×10^{-2} mol·L^{-1}) respectively. The mixture was diluted to 5 mL with Tris–HCl (pH = 7.4), too. Thus, samples were prepared in the concentration of NaCl at 0.0, 800, 1600, 2400, 4800, 7200, 9600, 12,000, 14,400, 16,800, 19,200, 21,600 and 24,000 $\times 10^{-6}$ mol·L^{-1}. One contained only compounds **1–7** (40×10^{-6} mol·L^{-1}) and DNA (45.68×10^{-6} mol·L^{-1}) as control, the others contained different concentration of NaCl but had the same concentration of compounds **1–7** and DNA. All the above solution was shaken for 30 min at room temperature. Fluorescence wavelengths and intensity areas of samples were also the same as Section 2.3.2.1.

2.3.3. CD Measurement

2 mL solution of herring sperm DNA (9.128×10^{-4} mol·L^{-1}) in PBS (pH = 7.4) was mixed with 0.0, 0.40, 0.80 and 1.20 mL of compounds **1–7** (2.00×10^{-4} mol·L^{-1}) respectively. The mixture was diluted to 5 mL with PBS (pH = 7.4). Thus, samples were prepared in the concentration of compounds **1–7** at 0.0, 16.0, 32.0 and 48.0 $\times 10^{-6}$ mol·L^{-1}. One contained only DNA (182.56×10^{-6} mol·L^{-1}) as control, the others contained different concentration of compounds **1–7** but had the same