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吩噻嗪-Corrole 镓(III)配合物的合成、荧光及其光断裂 DNA 性质

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摘要: 合成了吩噻嗪(PTZ)-corrole 二元体 1–3 及其镓(III)配合物 4–6。采用稳态吸收与稳态发射及时间分辨的瞬态光谱技术研究了这几种化合物的光物理特性。结合荧光量子产率和荧光寿命计算得到它们的辐射和无辐射速率常数。稳态吸收光谱表明: 几种二元体中, corrole 镓(III)单元表现出更强的 Soret 带和 Q 带。化合物 1–3 的荧光量子产率分别是 0.156、0.134 和 0.139, 辐射速率常数分别为 4.02×10^7 、 3.47×10^7 和 $2.89 \times 10^7 \text{ s}^{-1}$ 。化合物 4–6 的荧光量子产率分别是 0.502、0.443 和 0.494, 辐射速率常数分别为 20.90×10^7 、 16.78×10^7 和 $21.11 \times 10^7 \text{ s}^{-1}$ 。可见, 化合物 4–6 的荧光量子产率和辐射速率常数均高于化合物 1–3。然而, 化合物 4–6 的荧光寿命分别是 2.40、2.64 和 2.34 ns, 低于自由 corrole 1–3。琼脂糖凝胶电泳实验表明: 在光照的条件下, 这些吩噻嗪-corrole 镓(III)二元体化合物能够把超螺旋 DNA (form I) 切割成缺刻型 DNA (form II)。

关键词: Corrole; 吩噻嗪; 镓(III); 荧光; DNA

中图分类号: O644

Synthesis, Fluorescence and DNA Photocleavage Activity of Phenothiazine-Corrole Gallium(III) Complexes

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Abstract: Phenothiazine (PTZ)-corrole dyads 1–3 and their gallium(III) complexes 4–6 have been synthesized and characterized. The steady-state absorption and emission spectra and the time-resolved fluorescence decay profiles have been measured in toluene. The radiative and nonradiative rate constants have been obtained from the fluorescence quantum yields and monoexponential fluorescence lifetimes. The absorption spectra revealed that the gallium(III) corrole dyads exhibit stronger Soret bands and Q bands than free base corrole dyads. The fluorescence quantum yields of 1–3 are 0.156, 0.134, and 0.139, and the radiative rate constants are 4.02×10^7 , 3.47×10^7 , and $2.89 \times 10^7 \text{ s}^{-1}$, respectively. The fluorescence quantum yields of 4–6 are 0.502, 0.443, and 0.494, and the radiative rate constants are 20.9×10^7 , $16.78 \times$

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10^7 , and $21.11 \times 10^7 \text{ s}^{-1}$, which are obviously higher than those of the corresponding free base corroles. The lifetimes of **4–6** are 2.40, 2.64, and 2.34 ns, respectively, which are somewhat shorter than those of the corresponding free base corroles. Agarose gel electrophoresis shows that these gallium(III) corrole dyads could cleave supercoiled DNA (form I) to give nicked-circular DNA (form II) under irradiation.

Key Words: Corrole; Phenothiazine; Gallium(III); Fluorescence; DNA

1 Introduction

Metallocorroles have been applied in catalysis,^{1,2} medicinal applications,^{3–5} and recently in photophysics.^{6–10} Since the computational investigations suggest that gallium(III) may fit perfectly into the coordination core of corroles,¹¹ gallium(III) corroles have been received interest in recent ten years. The first reported corrole gallium(III) complex was synthesized by Gross,^{12,13} its X-ray structures, electrochemical and photophysical properties were also determined. Facile synthetic methodologies and high fluorescence yield allowing for the preparation of more gallium(III) corroles and more extensively properties have been determined.^{14–16} Amphiphilic gallium(III) corroles could form tightly bound noncovalent conjugates with human serum albumin.¹⁷ In addition, it has been discovered recently that these gallium(III) corroles could also be explored for tumor detection and elimination.¹⁸ Phenothiazine (**PTZ**) is an interesting chromophore recognized pharmaceutical compound, which has shown diverse biological activities such as neuroleptic, antiemetic, antihistamine and anthelmintic activities.^{19,20} Recently, we²¹ found that phenothiazine-corrole dyads **1–3** exhibited enhanced DNA photocleavage properties, high fluorescence quantum yield, and DNA binding activities. Although Ga(III) corroles exhibited potential application in medicinal chemistry,^{17,18} no report was found on the interaction between Ga(III) corrole complexes and DNA so far. In this paper, we report the fluorescence property and DNA photocleavage activity of *ortho*-, *meso*-, and *para*-phenothiazine-corrole gallium(III) complexes **4–6**, which are derived from free base corrole dyads **1–3**, respectively.

2 Experimental

2.1 Materials and methods

Tetraphenylporphyrin (TPP) was synthesized by Adler's method.²² Calf thymus deoxyribonucleic acid (CT DNA) was purchased from Sigma-Aldrich Corporation and pBR 322 plasmid DNA was purchased from TaKaRa Biotechnology Co., Ltd. (TaKaRa Dalian, China). All other reagents and solvents were reagent grade and used without further purification. Silica gel (100–200 mesh) were used for column chromatography. Reactions were monitored by thin layer chromatography and spectrophotometry. Mass spectra were obtained using a Bruker Esquire HCT PLUS mass spectrometer (Bruker Company, USA). ¹H-NMR spectra were recorded with a VARIAN 300 MHz NMR spectrometer in CDCl₃ (Varian Company, USA). Absorption spectra of all samples were measured by a Perkin

Elmer Lambda 850 UV-Vis Spectrometer (PE Company, USA). Fluorescence spectra were recorded by a Perkin Elmer LS55 Luminescence Spectrometer (PE Company, USA). The fluorescence decay curves were measured by a time-resolved fluorescence spectroscopic experimental setup. A Nd:YAG laser (EKSPLA PL2143) and an OPG system (EKSPLA PG401SH/DFG2-10) generated the laser pulse (420 nm, 10 Hz) with a full width at half maximum (FWHM) of 22 ps as a light source (EKSPLA Company, Lithuania). The fluorescence was collected with a pair of lenses with big caliber. After passing through a monochromator, it was recorded by a streak camera (Hamamatsu C1587) and a CCD (Hamamatsu C4742-95). The fluorescence lifetime can be determined with a 30 ps resolution by the deconvolution procedure. Photoirradiation was carried out using a simple system consisting of an 11 W fluorescence lamp placed 10 cm away from a sample compartment thermostatted in a water jacket at 25 °C. Supercoiled pBR 322 DNA (0.1 μg) was treated with phenothiazine-corrole gallium(III) complexes in 50 mmol · L⁻¹ tris-HCl, 18 mmol · L⁻¹ NaCl buffer, pH=7.2, and the solutions were incubated for 1 h in the dark, then irradiated. The samples were analyzed by electrophoresis for 2 h at 50 V and 30 mA in tris-HCl buffer containing 1% (mass fraction) agarose gel. The gel was stained with 1 μg mL⁻¹ ethidium bromide and then photographed under UV light (365 nm). All measurements were carried out at room temperature.

2.2 Synthesis

2.2.1 Synthesis of the phenothiazine-corrole dyads

Phenothiazine-corrole dyads **1–3** were prepared previously.²¹

2.2.2 Preparation of phenothiazine-corrole gallium(III) complex (**4**)

A solution of phenothiazine-corrole dyad **1** (19.9 mg, 21 μmol) in pyridine (10 mL) was added to a flask that contained a large excess (about 0.2 g) of flame-dried GaCl₃, and the reaction mixture was heated to reflux for 1 h under N₂, followed by evaporation of the solvent. The inorganic salts were separated by column chromatography on silica ($V_{\text{hexane}}:V_{\text{CH}_2\text{Cl}_2}:V_{\text{pyridine}}=100:50:0.5$, volume ratio), affording 17.0 mg (16.8 μmol, 80.0% yield) of the pyridine gallium(III) complex of **4**. ¹H-NMR (CDCl₃, 300 MHz): δ, 3.18–3.19 (m, 2H, pyridine-H), 5.48–5.49 (m, 2H, pyridine-H), 6.30–6.32 (m, 1H, pyridine-H), 7.16–7.21 (m, 2H, Ph), 7.28–7.33 (m, 2H, Ph), 7.36–7.40 (m, 2H, Ph), 7.55–7.60 (m, 3H, Ph), 7.64–7.66 (m, 1H, Ph), 7.75–7.80 (m, 1H, Ph), 8.01–8.04 (m, 1H, Ph), 8.62–8.64 (m, 2H, Ph), 8.82–8.84 (m, 4H, pyrrole-H), 9.21–9.23 (m, 2H, pyrrole-H); ¹⁹F-NMR (CDCl₃, 380 MHz): δ, -162.43 – -162.24

Fig.1 Structure and synthesis of phenothiazine-corrole gallium(III) complexes

(m, 4F), -153.91 (t, $J=44.1$ Hz, 2F), -138.06 – -137.95 (m, 4F); UV-Vis (toluene), $\lambda_{\max}$, unit in nm, (relative intensity): 288.0 (0.230), 423.0 (2.45), 574.0 (0.251), 598.0 (0.335); Atmospheric pressure chemical ionization MS (APCI-MS): 1014.1 [M-pyridine+H⁺].

2.2.3 Preparation of phenothiazine-corrole gallium(III) complex (5)

A solution of phenothiazine-corrole dyad **2** (19.9 mg, 21 μ mol) in pyridine (10 mL) was added to a flask that contained a large excess (about 0.2 g) of flame-dried GaCl₃, and the reaction mixture was heated to reflux for 1 h under N₂, followed by evaporation of the solvent. The inorganic salts were separated by column chromatography on silica ($V_{\text{hexane}}:V_{\text{CH}_2\text{Cl}_2}:V_{\text{pyridine}}=100:70:0.5$), affording 19.1 mg (18.9 μ mol, 90.0% yield) of the pyridine gallium(III) complex of **5**. ¹H-NMR (CDCl₃, 300 MHz): δ , 3.10–3.22 (m, 2H, pyridine-H), 5.87–5.92 (m, 2H, pyridine-H), 6.63–6.70 (m, 1H, pyridine-H), 7.18–7.23 (m, 2H, Ph), 7.30–7.35 (m, 2H, Ph), 7.38 (d, $J=8.4$ Hz, 2H, Ph), 7.56 (d, $J=9.1$ Hz, 1H, Ph), 7.67–7.75 (m, 3H, Ph), 7.96 (d, $J=8.4$ Hz, 2H, Ph), 8.77–8.82 (m, 6H, pyrrole-H), 9.20–9.21 (m, 2H, pyrrole-H); ¹⁹F-NMR (CDCl₃, 380 MHz): δ , -162.68 – -162.38 (m, 4F), -154.16 (t, $J=44.1$ Hz, 2F), -138.15 – -137.92 (m, 4F); UV-Vis (toluene), $\lambda_{\max}$, unit in nm, (relative intensity): 293.0 (0.209), 424.0 (2.59), 574.0 (0.245), 602.0 (0.366); APCI-MS: 1014.1 [M-pyridine+H⁺].

2.2.4 Preparation of phenothiazine-corrole gallium(III) complex (6)

A solution of phenothiazine-corrole dyad **3** (19.9 mg, 21 μ mol) in pyridine (10 mL) was added to a flask that contained a large excess (about 0.2 g) of flame-dried GaCl₃, and the reaction mixture was heated to reflux for 1 h under N₂, followed by evaporation of the solvent. The inorganic salts were separated by column chromatography on silica ($V_{\text{hexane}}:V_{\text{CH}_2\text{Cl}_2}:V_{\text{pyridine}}=100:70:0.5$), affording 19.1 mg (18.9 μ mol, 90.0% yield) of the pyridine gallium(III) complex of **6**. ¹H-NMR (CDCl₃, 300 MHz): δ , 2.88–2.98 (m, 2H, pyridine-H), 5.81–5.89 (m, 2H, pyridine-H), 6.62–6.70 (m, 1H, pyridine-H), 7.29–7.32 (m, 2H, Ph), 7.40–7.45 (m, 2H, Ph), 7.48–7.51 (m, 2H, Ph), 7.54 (d, $J=8.4$ Hz, 2H, Ph), 7.82–7.85 (m, 2H, Ph), 8.10 (d, $J=8.4$ Hz, 2H, Ph), 8.77–8.82 (m, 6H, pyrrole-H), 9.20–9.22 (m, 2H, pyrrole-H); ¹⁹F-NMR (CDCl₃, 380 MHz): δ , -162.59 – -162.45 (m, 4F), -154.18 (t, $J=44.1$ Hz, 2F), -138.28 – -138.02 (m,

4F); UV-Vis (toluene), $\lambda_{\max}$, unit in nm, (relative intensity): 293.0 (0.192), 424.0 (2.58), 574.0 (0.238), 603.0 (0.365); APCI-MS: 1014.1 [M-pyridine+H⁺].

3 Results and discussion

Phenothiazine-corrole dyads **1–3** was prepared according to previous published procedure in the literature.²¹ Phenothiazine-corrole gallium(III) complexes **4–6** could efficiently be obtained (Fig.1) in yields ranging from 80.0% to 90.0% according to the method reported by Gross.¹² Fig.2 shows the absorption spectra of phenothiazine-corrole dyad **3**, PTZ, and their gallium complexes **4–6** in toluene. The absorption spectra of **4–6** reveal a band at 290 nm corresponding to the phenothiazine entity, a Soret band and a *Q* band related to corrole unit. The $S_0 \rightarrow S_2$ (Soret band) and $S_0 \rightarrow S_1$ (*Q* band) transition of **4–6** are obviously enhanced compared to their free base corroles. This may be explained by the fact that the corrole macrocycle intends to be more planar or the changed acidity when the gallium is introduced,¹² resulting in the increase of the matrix element of the $\pi-\pi^*$ electronic transitions and stronger absorption.²³ This phenomenon is similar to the previously reported gallium(III) corroles.^{13,24} While the molar absorption coefficient (ϵ) of the PTZ is nearly identical to the phenothiazine entity of **3**, **4–6**, which means that the phenothiazine unit can be introduced without affecting the absorption characteristics of these gallium(III) corroles.

In our reported studies,²¹ we found that the phenothi-

Fig.2 UV-Vis absorption spectra of PTZ (phenothiazine-10-carbonyl chloride), **3** and **4–6** in toluene

Fig.3 Fluorescence emission spectra of TPP, complexes 3 and 4–6 in toluene at room temperature

Table 1 Fluorescence emission peak ($\lambda_{\max}$), quantum yields (Φ_f), life time (τ), radiative rate constant (k_f), and nonradiative rate constant (k_{nr}) data of complexes 1–6 in toluene at 295 K

Compound	$\lambda_{\max}/\text{nm}$	Φ_f^a	τ/ns	$10^{-7}k_f/\text{s}^{-1}$	$10^{-7}k_{nr}/\text{s}^{-1}$
1	647.5	0.156	3.88	4.02	21.75
2	654.0	0.134	3.86	3.47	22.44
3	656.0	0.139	4.81	2.89	17.90
4	602.8	0.502	2.40	20.90	20.70
5	608.8	0.443	2.64	16.78	21.10
6	609.2	0.494	2.34	21.11	21.63

^aTetraphenylporphyrin (TPP) was used as a standard ($\Phi_f=0.11$). $\lambda_{\text{ex}}=560$ nm

azine-corrole dyads exhibited higher fluorescence quantum yields compared to their corrole units. During the metallation by gallium, we noted a stronger red fluorescence. The fluorescence spectra of **3**, **4–6**, and TPP in toluene at room temperature upon excitation at the *Q* band (560 nm) are displayed in Fig.3 and the most relevant photophysical values are collected in Table 1. The luminescence peaks of our synthesized gallium complexes are all shifted to higher energies (ca 45 nm) as compared to their free base corroles, which maybe attributed to the larger energy between HOMO and LUMO of gallium(III) corroles.²³ The major points of interest are that three gallium(III) complexes exhibit higher fluorescence quantum yields than phenothiazine-corrole dyads, which can be explained by the more planar structure of metallic corroles.^{16,24,25} What's more, sample **4** exhibits the highest fluorescence quantum yields among the reported gallium(III) complexes we can find. Their lifetimes were also determined by the method described in ex-

Fig.4 Fluorescence decay curves of complexes 4–6 in toluene

Fig.5 Stability of supercoiled pBR 322 DNA with irradiation

Reaction mixtures (10 μL) contained 0.1 μg of plasmid DNA and 5% DMF. lanes 1–8: samples with 0, 30, 60, 90, 120, 150, 200, 250 min irradiation, respectively. *c*(form II): conversion of form I to form II

Fig.6 Agarose gel electrophoresis pattern for the cleavage of supercoiled pBR 322 DNA

Reaction mixtures (10 μL) contained 0.1 μg of plasmid DNA, 400 $\mu\text{mol}\cdot\text{L}^{-1}$ samples, and 5% DMF. lane 1: DNA alone (no *h\nu*); lane 2: DNA+**4** (no *h\nu*); lanes 3–5: complexes **4–6** with DNA, respectively (2 h *h\nu*).

perimental section. Samples were excited at 420 nm and the fluorescences were focused into the spectrometer before being collected by a streak camera and the collected wavelength was 608 nm. The resultant decay profiles for all samples could be explained satisfactorily in terms of a single exponential fit (Fig.4) and the calculated lifetimes (τ) are summarized in Table 1. The fluorescence lifetime decreases when the gallium is introduced. The emission rate constant (k_f) and nonemission rate constant (k_{nr}) constant can be determined from $k_f=\Phi_f/\tau$ and $k_{nr}=(1-\Phi_f)/\tau$.²⁶ For phenothiazine-corrole gallium(III) complexes **4–6**, the values of the k_f are 20.90×10^7 , 16.78×10^7 , and 21.11×10^7 s^{-1} . Note that the k_f of **4** and **5** are about 5-fold more than their free base corroles, and the k_f of **6** is about 7-fold more than that of **3**, while the value of k_{nr} is almost identical.

The DNA photocleavage activities were examined using supercoiled pBR 322 DNA. A mixture of corrole in DMF and the plasmid DNA in tris-HCl buffer (pH=7.2) was illuminated for 2 h at room temperature in a system consisting of an 11 W fluorescent lamp light source placed 10 cm away. The stability of supercoiled pBR 322 DNA with irradiation and agarose gel electrophoresis patterns for the photocleavage of DNA are shown in Fig.5 and Fig.6, respectively. Lane 1 is the control

DNA. Without illumination, all phenothiazine-corrole dyads or their gallium complexes exhibited no DNA cleavage activity (exemplified by lane 2). Phenothiazine-corrole dyads **1–3** exhibited 85%–100% conversion of supercoiled DNA (form I) to nicked-circular DNA (form II) at the concentration of 100 $\mu\text{mol}\cdot\text{L}^{-1}$ under illumination.¹² In contrast, their gallium complexes could cleave form I DNA to form II at the concentration of 400 $\mu\text{mol}\cdot\text{L}^{-1}$ and the DNA photocleavage activity follows an order of **4**<**5**=**6**. The descendent DNA photocleavage activities of **4–6** maybe explained by the reduction of singlet oxygen quantum yield (Φ_{Δ}) photosensitized by corroles. Phenothiazine-corrole dyads **1–3** show the Φ_{Δ} of 0.89–0.93, while we can not detect the singlet oxygen luminescence spectra of **4–6** in the same experimental conditions, which maybe because of the amazing radiative transition of **4–6**.

4 Conclusions

In summary, we synthesized three phenothiazine-corrole dyads **1–3** and their novel gallium(III) complexes **4–6**. The corrole unit exhibits stronger Soret band and Q band. The steady-state emission spectra and the temporal fluorescence decay profiles reveal that the fluorescence quantum yield and radiative decay constant are enhanced when the gallium is introduced. The quantum yields are 0.502, 0.443, and 0.494 for **4–6**, respectively. To our knowledge, the quantum yield of sample **4** is the highest among the reported gallium(III) complexes. The radiative and nonradiative rate constants were determined using a kinetic scheme: the values of radiative rate constant are 20.90×10^7 , 16.78×10^7 , and $21.11\times 10^7\text{ s}^{-1}$ for **4–6**, respectively, which are obviously higher than their free base corroles, but the nonradiative rate constant is almost identical. Agarose gel electrophoresis shows that these gallium(III) corroles could photocleave supercoiled DNA (form I) to nicked-circular DNA (form II) at the concentration of 400 $\mu\text{mol}\cdot\text{L}^{-1}$, which are the first observation of DNA photocleavage by corrole gallium(III) complexes. This information is of importance for potential utilization of corroles in photophysical and therapeutic applications.

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