Tetrahedron Letters 51 (2010) 3439–3442

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of phenothiazine-corrole dyads: the enhanced DNA photocleavage properties

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ARTICLE INFO

Article history:
Received 16 December 2009
Revised 26 April 2010
Accepted 27 April 2010

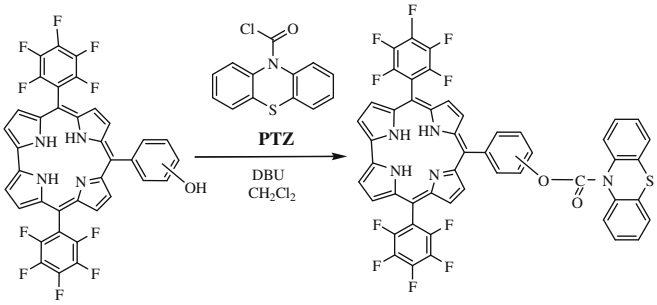
ABSTRACT

Three new phenothiazine-corrole dyads were prepared by the reaction of phenothiazine-10-carbonyl chloride and mono-hydroxyl triaryl corrole in the presence of DBU. As compared to corrole monomer, these phenothiazine-corrole dyads exhibit significant enhanced DNA photocleavage activity as compared to corrole monomer precursors.

In recent ten years, study on corrole has been received much attentions because of their potential applications in catalysis,[1] photophysics,[2] electrochemistry,[3] and particularly in biology.[4] Cationic corrole complexes showed unique activities when binding to DNA.[5] Free base corrole[6] and corrole copper complexes[7] are also able to photocleave DNA via singlet oxygen ($^1O_2$) mechanism. The $^1O_2$ quantum yield[8] and DNA binding[9] have been proved to be the key factors in photocleavage of DNA. Phenothiazine is a recognized pharmaceutical chromophore showing diverse biological activities including neuroleptic, antiemetic, antihistamine, anthelmintic[10] and DNA intercalation activities.[11] Thus, the introduction of phenothiazine (PTZ) into corrole may lead to the dyad with new photochemical and photobiological properties. Bearing this in mind, we herein wish to report the synthesis of a series of phenothiazine-corrole dyads (Scheme 1, **4**–**6**). Corrole dyads **4**–**6** exhibit higher fluorescence quantum yield and longer fluorescence lifetime than corresponding corrole units **1**–**3**. Agarose gel electrophoresis showed that these dyads exhibited significant enhanced DNA photocleavage activity.

The synthetic route for phenothiazine-corrole dyads is shown in Scheme 1. Mono-hydroxyl corrole **1**–**3** was prepared according to previous published procedure.[4a] Phenothiazine-corrole dyads **4–6** could be prepared efficiently by the reaction of corresponding mono-hydroxyl corroles **1–3** and phenothiazine-10-carbonyl chloride in dichloromethane at room temperature in the presence of DBU with yields of 60–95%.[12–14]

The affects of phenothiazine group on the absorption and luminescence spectra of three corrole dyads **4–6** are nearly identical. Figure 1 shows the UV–vis spectra of corrole precursor **3**, corresponding corrole dyad **6** and phenothiazine. The absorption spectra



1: *o*-OH; **2**: *m*-OH; **3**: *p*-OH **4**: *o*-PTZ; **5**: *m*-PTZ; **6**: *p*-PTZ

Scheme 1. The synthetic route for phenothiazine-corrole dyads.

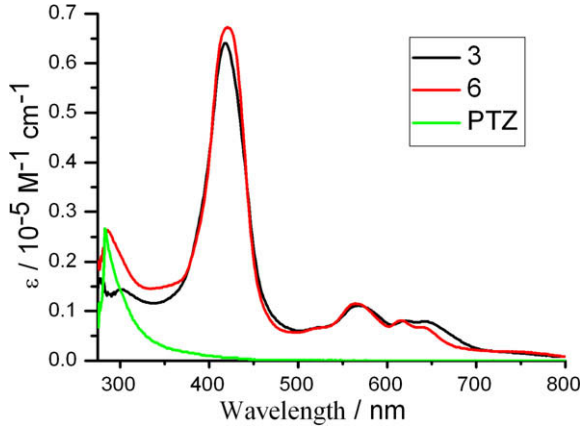


Figure 1. UV–vis spectra of **3**, **6** and **PTZ** in toluene (10^{-5} mol/L).

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doi:10.1016/j.tetlet.2010.04.112

of dyad **6** revealed a new band at 280 nm corresponding to the phenothiazine entity. While the Soret band (420 nm) and Q band (500–700 nm) were similar to that of free base corrole precursor. The spectra are essentially the superimposition of the absorption spectra of the components, pointing to a rather weak electronic coupling between corrole and phenothiazine chromophore. This allows an approach based on a localized description of the individual subunits.

Emission spectra and time resolved luminescence spectra of corrole precursor **3** and corrole dyad **6** are shown in Figures 2 and 3 respectively. Fluorescence quantum yields (Φ_f), maximum emission wavelength (λ_{max}), lifetime (τ) of all samples are summarized in Table 1. As can be seen, the luminescence band of the dyads are shifted to higher energies (3–4 nm) as compared to their parent monomers by selective excitation of the corrole unit at 560 nm. All PTZ-corrole dyads also exhibited higher fluorescence quantum yields and longer singlet exited state lifetime than monomer precursors. These observations are in contrast with other corrole-based multi-chromophoric dyads such as porphyrin,[17] naphthalene imide,[18] perylene bisimide,[19] perylenebisimide triphenylamine[20] and C_{60}-corrole.[21] The fluorescence quantum yields and lifetime of these reported corrole dyads were usually reduced by excitation of the corrole units because of the electron transfer (ET) process. This suggested there are no ET from corrole to PTZ chromophore in PTZ-corrole dyads when exciting corrole unit. The enhanced fluorescence quantum yield and lifetime may be caused by the introduction of phenothiazine unit, which is known as an excellent building block for impeding aggregation and intermolecular excimer formation.[22] Similar behavior was also observed in some phenothiazine-porphyrin dyads.[23] The fluorescence rate constant (k_f) and nonradiative rate constant (k_{nr}) of corrole dyads (Table 1) may be calculated from $k_f = \Phi_f/\tau$ and $k_{nr} = (1 - \Phi_f)/\tau$.[24] The values of k_{nr}/k_f for all of the corroles **1**–**6** are 6.94, 7.20, 7.62, 5.41, 6.47 and 6.19, respectively. It can be seen that values of the k_{nr}/k_f for mono-hydroxyl corroles **1**–**3** are obviously higher than that of corrole-phenothiazine dyads **4**–**6**. This suggests that the emission decay process of corroles is more favorable when a phenothiazine unit is introduced.

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. Agarose gel electrophoresis patterns for the photocleavage of DNA are shown in Figure 4. Lane 1 is the control DNA. Without illumination, all corrole or PTZ-corrole dyads exhibited no DNA cleavage activity (exampled by lane 2). Corrole **1**–**3** exhibited 54–58% conversion of supercoiled DNA

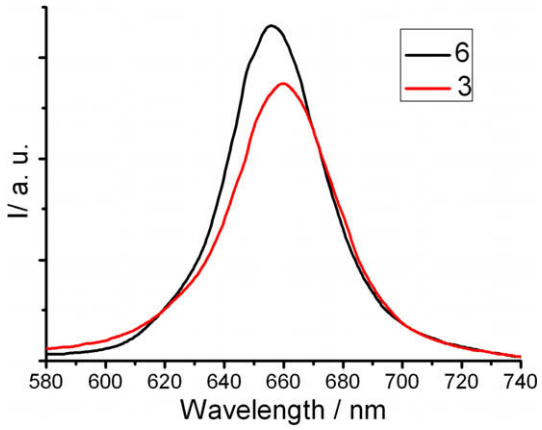

Figure 2. Emission spectra of **3** and **6** in toluene (10^{-5} mol/L) excited at 560 nm.

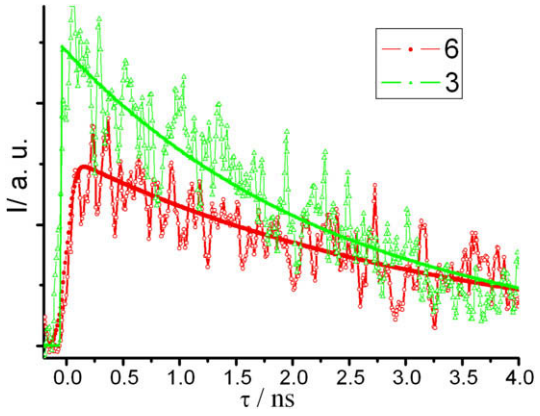

Figure 3. Time resolved luminescence spectra of **3**, **6** in toluene (10^{-5} mol/L). λ_{ex} = 560 nm.

Table 1
Fluorescence quantum yield (Φ_f), lifetime (τ), singlet oxygen luminescence quantum yields(Φ_Δ), fluorescence rate constant (k_f) and nonradiative rate constant (k_{nr}) in toluene, at room temperature

Compound	λ_{max} (nm)	Φ_f[a]	τ (ns)	k_f (10^7 s^{-1})	k_{nr} (10^7 s^{-1})	Φ_Δ[b]
1	650.5	0.126	2.45	5.14	35.67	0.72
2	656.0	0.122	2.47	4.94	35.55	0.74
3	660.0	0.116	2.11	5.50	41.90	0.75
4	647.5	0.156	3.88	4.02	21.75	0.89
5	654.0	0.134	3.86	3.47	22.44	0.91
6	656.0	0.139	4.81	2.89	17.90	0.93

[a] Tetraphenylporphyrin (TPP) was used as reference (Φ_f = 0.11).[15] λ_{ex} = 560 nm.
[b] TPP (Φ_Δ = 0.70) was used as reference.[16]

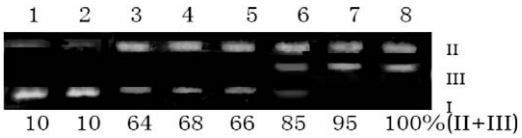

Figure 4. Agarose gel electrophoresis pattern for the cleavage of supercoiled pBR 322 DNA. Reaction mixtures (10 μL) contained 0.1 μg of plasmid DNA, 100 μmol/L samples and 5% DMF. Lane 1: DNA alone (no *hv*); lane 2: DNA+**1** (no *hv*); lane 3–8: sample **1**–**6** with DNA, respectively (*hv* 2 h).

(form I) to nicked-circular DNA (form II) under illumination (Fig. 4, lanes 3–5). In contrast, the dyads displayed enhanced photocleavage activity under the same conditions (Fig. 4, lanes 6–8). Supercoiled DNA might be completely degraded to nicked-circular DNA and linear DNA (form III) by **6** (Fig. 4, lane 8). Dyad **4** and **5** also exhibited efficient DNA cleavage activity (Fig. 4, lanes 6, 7). The DNA photocleavage activity follows an order of **4** < **5** < **6**. To further investigate the influence of PTZ group on singlet oxygen quantum yield (Φ_Δ) of corrole dyads, near-infrared luminescence measurements[25] was used to detect singlet oxygen. The luminescence of singlet oxygen generated by corroles excited at 560 nm is shown in Figure 5. The typical emission related to $^1O_2$ to $^3O_2$ transition is located at ca. 1280 nm. Quantum yield of $^1O_2$ could be estimated by using TPP (Φ_Δ = 0.70) as the reference[16] and the results are listed in Table 1. Singlet oxygen quantum yields of PTZ-corrole dyads are significantly higher than monomer corroles. Thus, the enhanced DNA photocleavage activity by PTZ-corrole dyads may be ascribed to the higher singlet oxygen quantum yields of them.

The interaction between PTZ-corrole dyads and DNA was also investigated by CD spectroscopy. CD is a sensitive method to detect

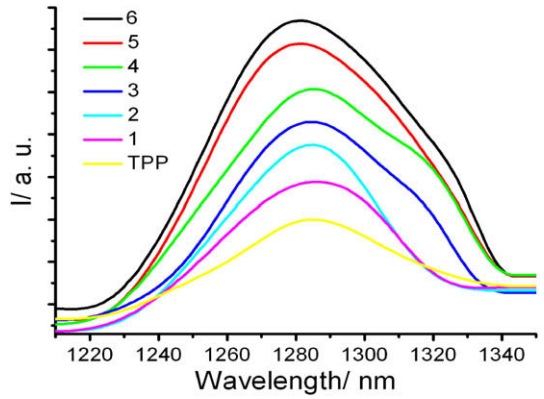

Figure 5. Luminescences of singlet oxygen generated by corrole photosensitizers in toluene. λ_{ex} = 560 nm.

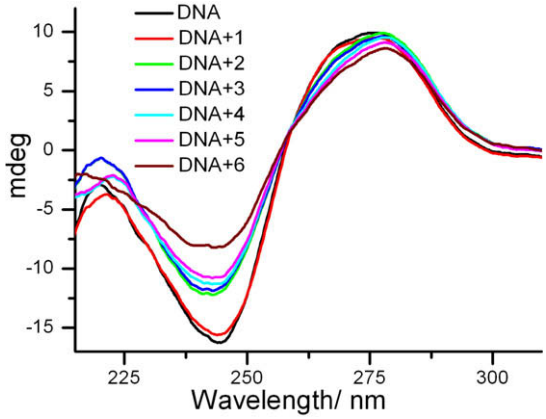

Figure 6. CD spectra of CT DNA (1.7 mM) in the absence and presence of samples **1**–**6** at ratio [corrole]/[DNA] = 0.4.

conformational change in nucleic acid duplexes.[26] CD spectrum of the CT DNA exhibited a positive band at 270 nm (base stacking) and a negative band at 240 nm (helix of B DNA).[26] Both of the positive (~275 nm) and negative (~245 nm) bands decreased in intensity with the increased concentration of the PTZ-corrole dyads (Fig. 6). This suggests that the DNA binding of the PTZ-corrole induces certain conformational changes, such as the conversion from a more B-like to a more C-like structure within the DNA molecule.[27] The largest decrease in the CD band intensity was observed by phenothiazine-corrole **6** at the same concentration. This implied that dyad **6** exhibited more effective binding than other samples. There are no obvious differences between sample **2**–**5** in the ability of perturbing the secondary structure of DNA, and **1** shows the least perturbation.

In conclusion, we have synthesized three new phenothiazine-corrole dyads. All these dyads exhibit higher fluorescence quantum yield and longer luminescence lifetime than monomer corrole precursors. The steady-state and time-resolved measurements suggest that introduction of phenothiazine into corroles could enhance emission decay process. The synthesized phenothiazine-corrole dyads also show significant enhanced DNA photocleavage activity as compared to their corrole monomer precursors, because of the higher light-induced singlet oxygen quantum yield by them. To our knowledge, this is the first report of the relationship between photophysical properties and DNA photocleavage of corrole based dyads.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Nos. 20771039, 20625205 and 20971046) and Natural Science Foundation of Guangdong Province (No. 9351027501000003).

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12. Procedure for the synthesis of corrole-phenothiazine dyads **5**. 10-(4-Hydroxylphenyl)-5,15-bis(pentafluorophenyl)corrole (**2**) (0.0433 g, 0.06 mmol) and phenothiazine-10-carbonyl chloride (0.0314 g, 0.12 mmol) were dissolved in dry CH_2Cl_2 (50 mL), 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) (35 μL, 0.24 mmol) was then added, and the solution was stirred at room temperature for 1 h. The reaction mixture was washed with saturated NaCl solution, dried (Na_2SO_4) and the crude compound was purified on a silica gel column using hexane/CH_2Cl_2 (3:1). Evaporation of the solvent yielded the title compound as a purple solid (0.0540 g, yield = 95%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.22 (t, J = 7.6 Hz, 2H, Ph), 7.32–7.36 (m, 2H, Ph), 7.42 (d, J = 3.6 Hz, 2H, Ph), 7.63 (d, J = 7.6 Hz, 1H, Ph), 7.75–7.77 (m, 3H, Ph), 8.02–8.04 (m, 2H, Ph), 8.56 (br s, 2H, pyrrole-H), 8.73 (br s, 4H, pyrrole-H), 9.10 (br s, 2H, pyrrole-H); ^{19}F NMR ($CDCl_3$, 400 MHz): δ ppm −161.69 (m, 4F), −152.73 (m, 2F), −137.79 (m, 4F); UV–vis (toluene), λ_{max}, nm (relative intensity): 296.0 (0.250), 420.0 (0.485), 565.0 (0.092), 615.0 (0.068); HR-MS: calcd exact mass ($C_{50}H_{24}F_{10}N_5O_2S$): 948.1491; found: 948.1309 [M+H$^+$].
13. Corrole-phenothiazine dyads **6** was obtained by using the same procedure described for **5**. A purple solid (0.0540 g, yield = 95%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.29 (t, J = 7.6 Hz, 2H, Ph), 7.44 (t, J = 7.6 Hz, 2H, Ph), 7.50 (d, J = 7.6 Hz, 2H, Ph), 7.62 (d, J = 7.6 Hz, 2H, Ph), 7.85 (d, J = 8.0 Hz, 3H, Ph), 8.17 (br s, 2H, Ph), 8.56 (br s, 2H, pyrrole-H), 8.71 (br s, 4H, pyrrole-H), 9.10 (br s, 2H, pyrrole-H); ^{19}F NMR ($CDCl_3$, 400 MHz): δ ppm −161.67 (m, 4F), −152.73 (m, 2F), −137.83 (m, 4F); UV–vis (toluene), λ_{max}, nm (relative intensity): 295.0 (0.269), 420.0 (0.676), 566.0 (0.120), 615.0 (0.087); HR-MS: calcd exact mass ($C_{50}H_{24}F_{10}N_5O_2S$): 948.1491; found: 948.1312 [M+H$^+$].
14. Procedure for the synthesis of corrole-phenothiazine dyads **4**. 10-(2-Hydroxylphenyl)-5,15-bis(pentafluorophenyl)corrole (**1**) (0.0433 g, 0.06 mmol) and phenothiazine-10-carbonyl chloride (0.1570 g, 0.60 mmol) were dissolved in dry CH_2Cl_2, DBU (35 μL, 0.24 mmol) was then added, and the solution was stirred at room temperature for 72 h. The reaction mixture was washed with saturated NaCl solution, dried (Na_2SO_4) and the crude compound was purified on a silica gel column using hexane/CH_2Cl_2 (4:1). Evaporation of the solvent yielded the title compound as a purple solid (0.0341 g, yield = 60%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.55 (d, J = 8.4 Hz, 1H, Ph), 7.63 (t, J = 7.2 Hz, 2H, Ph), 7.77 (d, J = 7.6 Hz, 1H, Ph), 7.80–7.84 (m, 2H, Ph), 8.10 (d, J = 7.2 Hz, 2H, Ph), 8.45–8.46 (m, 2H, Ph), 8.54 (s, 1H, Ph), 8.60–8.61 (m, 5H, 1H from Ph and 4H from pyrrole-H), 8.68 (s, 1H, pyrrole-H), 9.07 (s, 1H, pyrrole-H), 9.12–9.13 (m, 2H, pyrrole-H); ^{19}F NMR ($CDCl_3$, 400 Mz): δ ppm −161.69 (m, 4F), −152.72 (m, 2F), −137.80 (m, 4F); UV–vis (toluene), λ_{max}, nm (relative intensity): 296.0 (0.220), 420.0 (0.394), 566.0 (0.079), 615.0 (0.063); HR-MS: calcd exact mass ($C_{50}H_{24}F_{10}N_5O_2S$): 948.1491; found: 948.1379 [M+H$^+$].
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