Highly Efficient Photoinduced DNA Cleavage by Naphthopyrone Hydroperoxides

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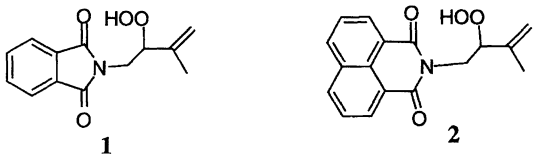
A variety of naphthopyrone hydroperoxides as novel photochemical DNA cleavers were synthesized and evaluated. Their photochemical DNA-cleaving abilities depend on skeleton arrangement of the naphthopyrone core and are much more efficient than those of the reported 1,8-naphthalenedicarboximide analog. The DNA-cleaving mechanism by these new hydroperoxides probably mainly involves hydroxyl radicals, indicating that naphthopyrone hydroperoxides may be able to serve as a new class of intercalating photo-Fenton reagents.

The development artificial photonucleases has received considerable interest due to their significant importance in molecular biology and human medicine.[1,2] Such molecules are chemically stable and activable by photoirradiation, particularly by a pulse of light. The advantage of such photoactivable DNA-cleaving molecules is that their action can be controlled within time and space by choosing proper irradiation methods. While some strategies for photoinduced DNA cleavage have been investigated, hydroxyl radical-generating molecules, the so-called photo-Fenton reagents,[2] are particularly attractive since hydroxyl radicals are particularly important in oxidation damage of biomolecules in the cellular system[3] and biochemical tools for the function and structure of nucleic acids.[4] Phthalimide hydroperoxides (e.g. **1**) were first reported as photo-Fenton reagents and DNA cleavers by Saito et al.[2b] (Chart 1). Later on, a new class of photo-Fenton reagents 1,8-naphthalenedicarboximide peroxides (e.g. **2**) were developed and showed higher DNA-cleaving ability.[2c,5] These molecules, designed to generate hydroxyl radicals, were shown to intercalate with DNA in the dark, and efficiently cleave DNA upon photochemical activation.[2c,5] However, their DNA-cleaving efficiency still remains to be improved. Naphthopyrones have been isolated from several kinds of natural sources and have shown a variety of interesting biological activities.[6] Although only a limited number of synthetic naphthopyrone derivatives have been described,[7] their DNA-intercalating ability was established,[8] indicating that naphthopyrones would be good candidates for the intercalating moiety in a new class of intercalating DNA cleavers. The efficient synthetic methodology for hydroxylnaphthopyrones developed recently in our laboratory would provide appropriate precursors for novel derivatives.[9] We herein report the synthesis and properties of naphthopyrone hydroperoxides as highly efficient photochemical DNA cleavers.



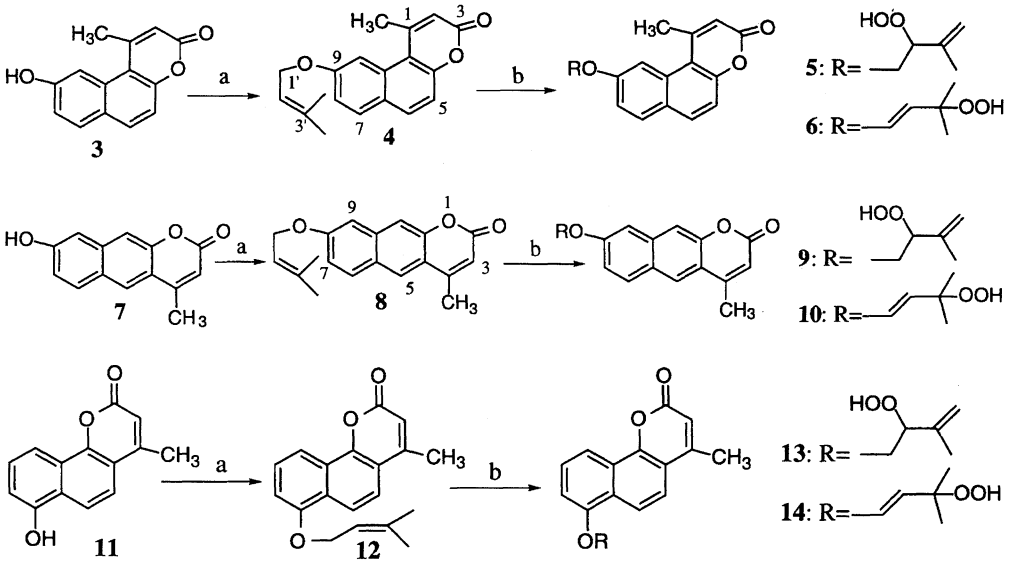
1 **2**

Chart 1.

Results and Discussion

The synthetic routes for naphthopyrone hydroperoxides are shown in Scheme 1. The hydroxylnaphthopyrones **3**, **7**,[9a] and **11**[9b] were readily prepared according to our previously reported procedures. In the presence of K_2CO_3, 3-methyl-2-butenyl bromide readily reacted with hydroxylnaphthopyrones **3**, **7**, and **11** to afford the corresponding ethers **4**, **8**, and **12**, respectively. The synthesis of target hydroperoxides were achieved by photooxygenations of corresponding prenylated ethers in the presence of TPP (tetraphenylporphyrine) as a sensitizer. Thus, the photooxygenation **4** yielded a mixture of **5** and **6**, which could be seperated by preparative TLC. Hydroperoxides **9**, **10**, **13**, and **14** were similarly synthesized. It was worth noting that only *E* conformation isomers of **6**, **10**, and **14** were produced as indicated by their characteristic doublet peaks at $\delta \approx 5.7$ and 6.9 ppm with a coupling of $J \approx 12.4$ in the ^{1}H NMR spectrum. In the course of purification of these hydroperoxides, we also found that **5**, **9**, and **13** were more stable than their corresponding isomers **6**, **10**, and **14**, respectively.

The DNA cleavage by these naphthopyrone peroxides were investigated using circular pUC 19 DNA and analyzed by agarose gel electrophoresis. None of the peroxides showed any DNA-cleaving activities without irradiation (data not shown), indicating that these compounds are inactive until triggered photochemically. Suprisingly, under irradiation of 365 nm light, all of the naphthopyrone peroxides cleaved DNA much more efficiently than the reported 1,8-naphthalenedicarboximide analog **2** (lane 3),



a) K_2CO_3, 3-methly-2-butenyl bromide, butanone; b) TPP, $h\nu$, dichloromethane.

Scheme 1.

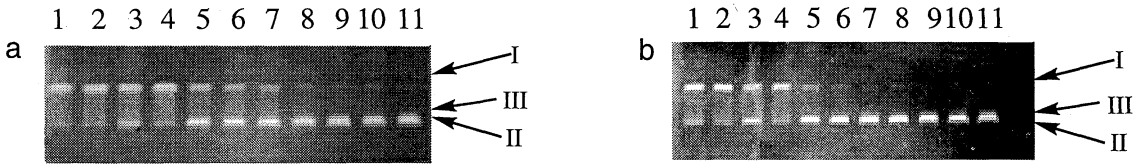


Fig. 1. Light-induced cleavage of DNA by naphthopyrone hydroperoxides. Supercoiled DNA runs at position I, nicked DNA at position II, and linear DNA at position III. pUC19 DNA (1.0 μg) was incubated in 10 μl of 1×TBE with drugs (400 μM concentration) at room temperature in the dark for 2 h, and irradiation for 20 min (a), 35 min (b) at 365 nm. The samples were analyzed by gel electrophoresis in 1% agarose and the gel was stained with ethidium bromide. Lane 1: DNA without irradiation, Lane 2: DNA with irradiation, Lane 3: **2**, 4: **4**, 5: **5**, 6: **6**, 7: **5** : **6** ≈ 1 : 1, 8: **9**, 9: **10**, 10: **13**, 11: **14**.

suggesting that naphthopyrones bind to DNA with higher affinity than the 1,8-naphthalenedicarboximide moiety. As shown in Fig. 1a, under the conditions of low concentration (micromolar level) and short irradiation time (20 min), naphthopyrone peroxides **5**, **6**, **9**, **10**, **13**, and **14** efficiently converted Form I DNA (covalently closed circular) into Form II (nicked circular) DNAs in a typical single-strand cleavage. The relative amount of cleavage in Fig. 1a suggests that compounds have the following DNA-cleaving potencies: **14** > **10** ≈ **9** ≈ **13** > **6** > **5** ≫ **2** ≫ **4**. Interestingly, isomers **14**, **10**, and **6** have higher DNA-cleaving efficiency than their corresponding isomers **13**, **9**, and **5** respectively, implying that these hydroperoxides cleave DNA through the same mechanism. Longer irradiation time caused more intense DNA cleavage. As shown in Fig. 1b, Form I DNA was almost completely converted; and Form III DNA (resulting from double-strand cuts or proximal single-strand cuts on opposite strands) was also observed after irradiation for 35 min. It is noteworthy that naphthopyrone **4** (lane 4), a precursor of **5** and **6**, couldn't cleave DNA at all under the same experimental conditions, indicating that hydroperoxide moieties are indispensable for the direct DNA cleavege by these drugs, and the direct DNA cleavage mechanism probably mainly involved hydroxyl radicals.[2,5] An equally plausible alternative pathway involves photoinduced electron transfer.[10]

In summary, the successful development of naphthopyrone hydroperoxides as a novel class of photochemical DNA-cleaving agents was described, and their DNA-cleaving efficiency was dependent on the skeleton arrangement of naphthopyrone cores and much higher than that of reported analogs. While the detailed mechanism of the photochemical DNA cleavage by these molecules remains to be established, their excellent DNA-cleaving capability suggests the possibly significant potentials in molecular biology and human medicine. This is the first demonstration that improvement of DNA-cleaving ability can be done by incorporation of naphthopyrone intercalating moiety.[11]

Experimental

General. Melting points were taken on a digital melting point apparatus WRS-1 made in Shanghai and are uncorrected. Infrared spectra were recorded on a Nicolet FT IR-20sx or Spectrometor 7650 made in Shanghai, mass spectra on a Hitachi M 80 or HP5989A, ^{1}H NMR on a Bruker AM-300 or Brucker DRX-400 using $CDCl_3$ or TMS as an internal standard. Combustion analysis for elemental composition was done on an Italy MOD. 1106 analyzer run by the analysis center of the East China University

of Science and Technology. Absorption spectra were measured in absolute ethanol on a Shimadzu UV-265, fluorescence spectra on a Perkin Elmer LS 50. Commercial reagents and solvents were purchased from standard chemical suppliers and used without further purification.

9-(3-Methyl-2-butenyloxy)-1-methylnaphtho[2,1-*b*]pyran-3-one (4). Also as a typical procedure for preparations of **8** and **12**. A mixture of 1.50 g (6.60 mmol) of **3**, 1.0 ml (8.42 mmol) of 3-methyl-2-butenyl bromide, and 1.0 g (7.25 mmol) of anhydrous K_2CO_3 in 30 ml of butanone was stirred for 1.5 h, cooled, and then 50 ml of ice water was added. The precipitates were collected by filtration and washed with water. After recrystallization from ethyl acetate, 1.28 g of needles **4** was obtained in 91% yield. Mp 130.5—131.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.80 (s, 3H, 3′-CH_3), 1.83 (s, 3H, 3′-CH_3), 2.91 (d, 3H, J = 0.9 Hz, 1-CH_3), 4.68 (d, 2H, J = 6.6 Hz, 1′-CH_2–), 5.55 (m, 1H, 2′-H), 6.34 (d, 1H, J = 0.9 Hz, 2-H), 7.22 (dd, 1H, J_{AX} = 8.9 Hz, J_{AB} = 2.3 Hz, 8-H), 7.31 (d, 1H, J = 8.9 Hz, 5-H), 7.81 (d, 1H, J = 8.9 Hz, 7-H), 7.88 (d, 1H, J = 8.9 Hz, 6-H), 7.96 (d, 1H, J = 2.3 Hz, 10-H). MS (El, 70 eV) *m/z* (%) = 294 (7.3) [M], 226 (100), 198 (78.5). UV (ethanol) λ_{max} (log ε) 348 (3.929) nm. Fl (ethanol) λ_{max} = 447 nm. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16%. Found: C, 77.50; H, 6.16%.

8-(3-Methyl-2-butenyloxy)-4-methylnaphtho[2,3-*b*]pyran-2-one (8). Mp 169.5—170.3 °C ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.80 (s, 3H, 3′-CH_3), 1.84 (s, 3H, 3′-CH_3), 2.53 (d, 3H, J = 1.2 Hz, 4-CH_3), 4.66 (d, 2H, J = 6.7 Hz, 1′-CH_2–), 5.58 (m, 1H, 2′-H), 6.28 (d, 1H, J = 1.2 Hz, 3-H), 7.13 (d, 1H, J_{BA} = 2.4 Hz, 9-H), 7.16 (dd, 1H, J_{AX} = 9.0 Hz, J_{AB} = 2.4 Hz, 7-H), 7.58 (s, 1H, 10-H), 7.81 (d, 1H, J = 9.0 Hz, 6-H), 7.99 (s, 1H, 5-H). Ms (El, 70 eV) *m/z* (%) = 294 (3.5) [M], 226 (100), 198 (36.3). UV (ethanol) λ_{max} (log ε) 278 (4.295), 287 (4.336), 347 (4.228) nm. Fl (ethanol) λ_{max} = 469 nm. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16%. Found: C, 77.61; H, 6.18%.

7-(3-Methyl-2-butenyloxy)-4-methylnaphtho[1,2-*b*]pyran-2-one (12). Mp 139.6—139.8 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.80 (s, 3H, 3′-CH_3), 1.84 (s, 3H, 3′-CH_3), 2.52 (s, 3H, 4-CH_3), 4.72 (d, 2H, J = 6.6 Hz, 1′-CH_2–), 5.61 (t, 1H, J = 6.6 Hz, 2′-H), 6.36 (s, 1H, 3-H), 6.98 (d, 1H, J = 7.7 Hz, 8-H), 7.50 (d, 1H, J = 8.4 Hz, 10-H), 7.54 (d, 1H, J = 8.7 Hz, 5-H), 8.12 (t, 2H, 9-H, 6-H). MS (El, 70 eV) *m/z* (%) = 294 (6.7) [M], 226 (100), 198 (54). UV (ethanol) λ_{max} (log ε) 285 (4.483), 304 (3.892), 363 (3.668), 379 (3.549) nm. Fl (ethanol) λ_{max} = 451 nm. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16%. Found: C, 77.42; H, 6.14%.

9-(2-Hydroperoxy-3-methyl-3-butenyloxy)-1-methylnaphtho[2,1-*b*]pyran-3-one (5) and 9-(3-Hydroperoxy-3-methyl-1-butenyloxy)-1-methylnaphtho[2,1-*b*]pyran-3-one (6). Also as a typical procedure for preparations of other naphthopyrone hydroperoxides. A solution of 200 mg (0.68 mmol) of **4** and 5 mg of tetraphenylporphyrine (TPP) in 40 ml of CH_2Cl_2 was irradiated externally by means of a sodium lamp (100 W) at −30±5 °C for 1.5 h while passing a continuous slow stream of dry oxygen gas through the solution. After the removal of the solvent, the residue was subjected to PTLC to afford 30 mg of **5** and 10 mg of **6** in 24% total yield.

5: IR (Nujol®) 3208, 2957, 2924, 2871, 2854, 1689, 1624, 1549, 1466, 1432, 1377, 1369, 1359, 1230, 1186, 1139, 954, 850, 845, 829, 721, 536 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.90 (s, 3H, 3′-CH_3), 2.92 (s, 3H, 1-CH_3), 4.21—4.33 (m, 2H, 1′-CH_2), 4.86 (dd, 1H, 2′-H), 5.19 (s, 1H, 4′-H), 5.21 (s, 1H, 4′-H), 6.35 (s, 1H, 2-H), 7.23—7.35 (m, 2H, 8-H, 5-H), 7.84 (d, J = 9.0 Hz, 1H, 7-H), 7.90 (d, J = 8.9 Hz, 1H, 6-H), 7.98 (d, J = 2.0 Hz, 1H, 10-H), 9.95 (s, 1H, 2′-OOH). HREIMS for $C_{19}H_{18}O_5$, Calcd for: M, 326.1154. Found: *m/z* 326.1150. MS (El, 70 eV) *m/z* (%) = 326 (10.0) [M], 308 (38.4), 226 (80.3), 198 (100), 181 (37.9), 169 (34.1), 152 (44.6).

6: ^{1}H NMR (CD_3COCD_3, 400 MHz) δ = 1.44 (s, 6H, 3′-(CH_3)$_2$), 2.98 (d, 3H, J = 1.1 Hz, 1-CH_3), 5.67 (d, 1H, J = 12.4 Hz, 2′-H), 6.39 (d, 1H, J = 1.1 Hz, 2-H), 6.95 (d, J = 12.4 Hz, 1H, 1′-H), 7.38 (dd, 1H, J_{AX} = 8.9 Hz, J_{AB} = 2.2 Hz, 8-H), 7.40 (d, 1H, J = 8.8 Hz, 5-H), 8.07 (d, 1H, J_{XA} = 8.9 Hz, 7-H), 8.15 (d, 1H, J = 8.8 Hz, 6-H), 8.22 (d, 1H, J_{AB} = 2.2 Hz, 10-H). HRFABMS for $C_{19}H_{18}O_5$, Calcd for: M, 326.1154. Found: *m/z* 326.1156.

9-(2-Hydroperoxy-3-methyl-3-butenyloxy)-4-methylnaphtho[2,3-*b*]pyran-2-one (9) and 9-(3-Hydroperoxy-3-methyl-1-butenyloxy)-4-methylnaphtho[2,3-*b*]pyran-2-one (10). 53% total yield.

9: 45 mg. IR (Nujol®) 3290, 3059, 2957, 2924, 2871, 2854, 1723, 1630, 1483, 1467, 1403, 1377, 1360, 1239, 1187, 1149, 928, 893, 888, 874, 721, 538 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 1.91 (s, 3H, 3′-CH_3), 2.54 (d, 3H, J = 1.0 Hz, 4-CH_3), 4.25 (m, 2H, 1′-H), 4.86 (m, 1H, 2′-H), 5.19 (s, 1H, 4′-H), 5.22 (s, 1H, 4′-H), 6.35 (d, 1H, J = 1.0 Hz, 3-H), 7.14 (dd, J_{AX} = 9.0 Hz, J_{AB} = 2.5 Hz, 1H, 7-H), 7.21 (d, 1H, J_{BA} = 2.5 Hz, 9-H), 7.58 (s, 1H, 10-H), 7.83 (d, J_{XA} = 9.0 Hz, 1H, 6-H), 8.01 (s, 1H, 5-H), 9.95 (s, 1H, 2′-OOH). ^{1}H NMR (CD_3COCD_3, 300 MHz) δ = 1.88 (s, 1H, 3′-CH_3), 2.58 (d, 3H, J = 1.0 Hz, 4-CH_3), 4.32 (m, 2H, 1′-H), 4.76 (t, 1H, 2′-H), 5.08 (t, 1H, 4′-H), 5.16 (d, 1H, J = 1.0 Hz, 4′-H), 6.32 (d, 1H, J = 1.0 Hz, 3-H), 7.20 (dd, 1H, J_{AX} = 9.1 Hz, J_{AB} = 2.4 Hz, 7-H) 7.42 (d, 1H, J_{BA} = 2.4 Hz, 9-H), 7.66 (s, 1H, 10-H), 8.00 (d, 1H, J_{XA} = 9.1 Hz, 6-H), 8.31 (s, 1H, 5-H). MS (El, 70 eV) *m/z* (%) = 326 (13.74) [M], 308 (21.16) [M-18], 293 (20.0) 226 (100), 198 (47.3), 181 (16.1) 169 (26.7), 152 (29.9). HREIMS for $C_{19}H_{18}O_5$, Calcd for $C_{19}H_{18}O_5$: M, 326.1154. Found: *m/z* 326.1154.

10: 43 mg. ^{1}H NMR (CD_3COCD_3) δ = 1.43 (s, 6H, 3′-CH_3), 2.59 (d, J = 1.1 Hz, 3H, 4-CH_3), 5.67 (d, J = 12.5 Hz, 1H, 2′-H), 6.35 (d, 1H, J = 1.1 Hz, 3-H), 7.01 (d, 1H, J = 12.5 Hz, 1′-H), 7.29 (dd, 1H, J_{AX} = 9.1 Hz, J_{AB} = 2.4 Hz, 7-H), 7.56 (d, 1H, J_{BA} = 2.4Hz, 9-H), 7.71 (s, 1H, 10-H), 8.05 (s, 1H, 3′-OOH), 8.09 (d, 1H, J_{XA} = 9.1 Hz, 6-H), 8.36 (s, 1H, 5-H). HRFABMS for $C_{19}H_{18}O_5$, Calcd for $C_{19}H_{18}O_5$: M, 326.1154. Found: *m/z* 326.1153.

9-(2-Hydroperoxy-3-methyl-3-butenyloxy)-4-methylnaphtho[1,2-*b*]pyran-2-one (13) and 9-(3-Hydroperoxy-3-methyl-1-butenyloxy)-4-methylnaphtho[1,2-*b*]pyran-2-one (14). 63% total yield.

13: 55 mg. IR (Nujol®) 3296, 2957, 2923, 2871, 2853, 2730, 1711, 1564, 1502, 1467, 1378, 1244, 1101, 721 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.92 (s, 3H, 3′-CH_3), 2.51 (d, 3H, J = 1.1 Hz, 4-CH_3), 4.34 (m, 2H, 1′-H), 4.93 (m, 1H, 2′-CH–), 5.19 (s, 1H, 4′-H), 5.24 (d, 1H, 4′-H), 6.38 (d, 1H, J = 1.1 Hz, 3-H), 7.00 (d, J = 7.8 Hz, 1H, 8-H), 7.49—7.58 (m, 2H, 9-H, 5-H), 8.07—8.15 (m, 2H, 6-H, 10-H). HRFABMS for $C_{19}H_{18}O_5$, Calcd for $C_{19}H_{18}O_5$: M, 326.1154. Found: *m/z* 326.1155.

14: 53 mg, ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.48 (s, 6H, 3′-CH_3), 2.54 (d, 3H, J = 1.0 Hz, 4-CH_3), 5.65 (d, J = 12.4 Hz, 1H, 2′-H), 6.40 (d, 1H, J = 1.0 Hz, 3-H), 6.88 (d, J = 12.4 Hz, 1H, 1′-H), 7.15 (d, 1H, J = 7.8 Hz, 8-H), 7.54—7.63 (m, 2H, 9-H, 5-H), 8.14 (d, 1H, J = 8.6 Hz, 6-H), 8.24 (d, 1H, J = 8.7 Hz, 10-H), 8.36 (s, 1H, 3′-OOH). HRFABMS for $C_{19}H_{18}O_5$, Calcd for $C_{19}H_{18}O_5$: M, 326.1154. Found: *m/z* 326.1153.

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