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Two new anthraquinone photoreactions

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Abstract

Two new photochemical reactions of 1-allyloxy-9,10-anthraquinones have been discovered. Both reactions involve initial photoinduced hydrogen abstraction and subsequent intramolecular electron transfers. The reactions were discovered as part of a project investigating the utility of intramolecular abstraction/SET processes for the release of biologically active aldehydes. The expected photochemistry for these compounds has been used to prepare *trans*-4-hydroxy-2-nonenal in 91% yield. However, under certain conditions, a number of unexpected reaction pathways became important. The first reaction included a remarkable C–C bond formation; mechanistic possibilities are suggested. The second reaction involved a 6-*endo* cyclization of a photochemically generated phenolic radical on a tethered alkene, followed by an unprecedented electron transfer from a secondary carbon-centered radical to a semiquinone radical. The resulting carbocation was then trapped by solvent. In one molecule, both reactions were observed, along with a third photoinduced Claisen rearrangment.

Keywords: Electron transfer; Radical cyclization; Hydrogen abstraction; Anthraquinone; *trans*-4-Hydroxy-2-nonenal

1. Introduction

Hydrogen abstraction and electron transfer processes are common themes in organic photochemistry and are of general interest to both physical organic and synthetic chemists [1]. These reaction pathways are useful both in synthesis and as mechanistic probes [2]. Often, transformations that can not occur in the ground state proceed efficiently via excited states. Quinones are efficient hydrogen atom abstractors and electron acceptors [3]. In some cases, both mechanisms operate in sequence to provide interesting chemistry not otherwise accessible. This facet of quinone photochemistry has been exploited in the synthesis of a variety of angucyclinones [4] and in the photorelease of bioactive aldehydes [5].

An example of a reaction in which both hydrogen abstraction and electron transfer play a key role is the intramolecular photodealkylation of 1-alkoxy-9,10-anthraquinones (e.g. **1**) that has been well documented by Blankespoor and coworkers (Scheme 1) [6–9]. Irradiation of **1** leads initially to intramolecular hydrogen abstraction to produce **2**. This is followed by a fast electron transfer that gives zwitterion **3**. The zwitterion can be trapped by a nucleophile, usually solvent, to produce acetal **4**, which is relatively stable to hydrolysis [6]. However, upon oxidation of hydroquinone **4** to anthraquinone, **5**, hydrolysis occurs readily [6]. The result is a 1-hydroxyanthraquinone, **6**, and an aldehyde, **7**.

In addition to mechanistic and kinetic studies, this chemistry has been used as an efficient means of preparing aldehydes in both solution and solid-phase [8,9]. Our interest in this chemistry arises from a desire to photorelease bioactive aldehydes [10,11]. Many bioactive aldehydes are α,β-unsaturated aldehydes; photorelease of such aldehydes from 1-allyloxy-9,10-anthraquinones had not been described until an earlier communication from our laboratory [5]. Prior to embarking on a full study of these compounds, we examined the photochemistry of **8** under both aerobic and anaerobic conditions. Along with the expected oxidative dealkylation, we discovered two new photoreactions. The details of this chemistry are reported below.

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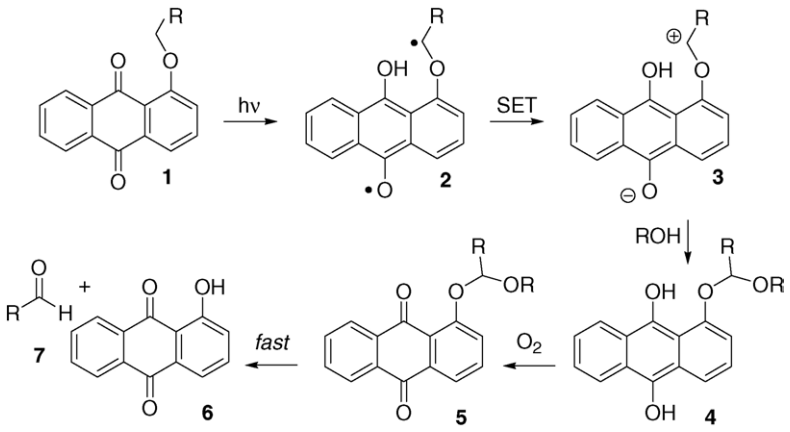


Scheme 1. Mechanism of photodealkylation of 1-alkoxy-9,10-anthraquinones.

2. Experimental

2.1. General methods

Melting points are uncorrected. ^{1}H NMR (300, 500 MHz) and ^{13}C NMR (75, 125 MHz) spectra were recorded on a Bruker Avance 300 MHz and 500 MHz spectrometers. Unless otherwise indicated, all reagents and solvents were obtained commercially and used without further purification: 1-hydroxy-9,10-anthraquinone was purchased from TCI America; all other compounds were purchased from Sigma–Aldrich, made using literature methods or prepared as described below. Tetrahydrofuran was dried via alumina column. CH_2Cl_2 was distilled over calcium hydride. Analytical thin-layer chromatography was performed on silica gel (250 μm thickness doped with fluorescein) unless otherwise indicated. Preparative thin-layer chromatography was conducted using 1000 μm silica plates doped with fluorescein. The chromatograms were visualized with UV light (254 nm or 366 nm) unless otherwise indicated. Column chromatography was performed using silica gel (60 Å) or alumina (neutral, 58 Å). Gas chromatography was carried out on an Agilent 6890GC with a Supelco β-Dex fused silica column (30 m × 0.25 mm × 0.25 μm). CCDC 262656 and 262657 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

2.2. Synthesis

2.2.1. 1-(3′-Methyl-2′-butenyloxy)-9,10-anthraquinone **8**

To a solution of 1-hydroxy-9,10-anthraquinone (224 mg, 1.00 mmol) and triphenylphosphine (328 mg, 1.25 mmol) in THF was added 3-methyl-2-buten-1-ol (0.150 mL, 1.50 mmol) and di-isopropyl-azodicarboxylate (DIAD) (0.345 mL, 1.75 mmol). Upon adding DIAD, the solution turned a rust-orange color. The flask was kept under argon and stirred at room temperature for 4 h. The crude reaction mixture was concentrated and purified immediately using flash column chromatography (silica gel) with an ethyl acetate/hexanes mobile phase (20% ethyl acetate). Anthraquinone **8** was isolated in 95% yield as a yellow powder (277 mg, 0.95 mmol). mp 120.0–121.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79 (s, 3H), 1.82 (s, 3H), 4.77–4.79 (d, J = 6.4 Hz, 2H), 5.58–5.64 (m, 1H), 7.32–7.35 (dd, J = 0.9, 8.5 Hz, 1H), 7.67–7.80 (m, 3H), 7.95–7.97 (dd, J = 1.1, 7.7 Hz, 1H), 8.22–8.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.5, 182.2, 159.7, 138.3, 135.8, 135.1, 134.7, 134.1, 133.1, 132.6, 127.2, 126.5, 121.9, 119.7, 119.2, 66.7, 25.8, 18.4. Anal. calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.04; H, 5.48. HRMS calcd for $C_{19}H_{16}O_3Na^+$: 315.09916. Found: 315.10047.

2.2.2. 1-(4-Hydroxy-2-nonenyloxy)-2-propyl-9,10-anthraquinone **20**

To a solution of 4-bromocrotonaldehyde [12] (53.7 mmol) in THF (80 mM, 671 mL) cooled to 0 °C was added dropwise a solution of pentyl magnesium bromide (1.15eq, 61.8 mmol) via an addition funnel. The reaction mixture turned a deep yellow color after 15 min. The reaction was quenched with water (200 mL), extracted with ethyl acetate (4 × 300 mL), dried with $MgSO_4$, and conc. in vacuo to give a pale brown oil (1-bromo-2-nonen-4-ol, 9.80 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87–0.91 (m, 3H), 1.22–1.44 (m, 6H), 1.49–1.54 (m, 2H), 1.57 (bs, 1H) 3.96 (d, J = 7.2 Hz, 2H), 4.11–4.18 (m, 1H), 5.79 (dd, J = 15.3, 6.0 Hz, 1H), 5.91 (dt, J = 15.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 126.4, 71.6, 36.9, 32.1, 31.6, 24.9, 22.5, 13.9. Anal. calcd for $C_9H_{16}OBr$: C, 48.88; H, 7.75; Br, 36.13. Found: C, 49.13; H, 7.86; Br, 35.86.

To a solution of 1-hydroxy-2-propyl-9,10-anthraquinone (5.26 mmol) in 2:1 THF:DMF (53 mL, 0.1 M) was added TBAF (1eq, 5.26 mmol). 1-Bromo-2-nonen-4-ol (0.5eq, 2.62 mmol) was added to the dark purple solution. The reaction mixture was stirred at room temperature for 5 h and

was complete by TLC (9:1 hexanes:EtOAc). The reaction was quenched with water (50 mL), extracted with EtOAc (3 × 50 mL), dried with $MgSO_4$, and conc. in vacuo. The crude product was chromatographed on silica (9:1 hexanes:EtOAc) and recystrallized from acetic acid and water to give a pale yellow powder (683.0 mg, 64%). mp: 94.0–95.0 °C. IR (NaCl, cm^{-1}) 3683, 3610, 3447, 3019, 2960, 2930, 2858, 1727, 1690. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88–0.92 (m, 3H), 1.00 (t, J = 7.4 Hz, 3H),1.25–1.59 (m, 8H), 1.65 (bs, 1H) 1.63–1.76 (m, 2H), 2.76 (t, J = 7.7 Hz, 2H), 4.18–4.25 (m, 1H), 4.54 (d, J = 5.8 Hz, 2H), 5.93 (dd, J = 15.5, 6.0 Hz, 1H), 6.10 (dtd, J = 15.5, 5.8, 0.9 Hz, 1H), 7.62 Hz (d, J = 7.9 Hz, 1H), 7.72–7.81 (m, 2H), 8.09 (d, J = 7.9 Hz, 1H). 8.23–8.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.1, 182.8, 157.4, 145.4, 137.3, 135.6, 134.8, 134.1, 133.7, 133.4, 132.6, 137.2, 126.6, 126.0, 125.8, 123.5, 74.3, 72.2, 37.1, 32.5, 31.7, 25.0, 23.3, 22.6, 14.1, 14.0. HRMS calcd for $C_{26}H_{30}O_4Na^+$: 429.203628. Found: 429.20143. Anal. calcd for $C_{26}H_{30}O_4$: C, 76.82; H, 7.44. Found: C, 76.54; H, 7.44.

2.2.3. 2-Propyl-1-(3,3′-dimethyl-2-butenyl)oxy-9,10-anthraquinone **23**

To a mixture of 1:1 DMF:THF (0.103 M, 15 mL) was added 1-hydroxy-2-propyl-9,10-anthraquinone [8] (1.55 mmol, 412 mg). Upon addition of TBAF (4.64 mmol), the solution turned a dark purple. 1-Bromo-3-methyl-2-butene (1.50 mmol) was added, and the reaction was stirred for 6.7 h. The reaction was quenched with H_2O and extracted with EtOAc (3 × 50 mL). The organic layers were combined and conc. in vacuo. The residue was chromatographed on silica (4:1 hexanes:EtOAc) to give a yellow powder (370.7 mg, 72%). mp 79.0–80.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (t, J = 7.35 Hz, 3H), 1.63–1.78 (m, 2H), 1.78 (s, 3H), 1.82 (s, 3H), 2.77 (t, J = 7.72, 2H), 4.53 (d, J = 7.16 Hz, 2H), 5.68–5.75 (m, 1H), 7.61 (d, J = 7.91, 1H), 7.71–7.81 (m, 2H), 8.05–8.10 (d, J = 7.91 Hz, 1H), 8.23–8.31 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.2, 182.8, 157.8, 145.6, 138.5, 135.4, 134.9, 134.0, 133.7, 133.3, 132.7, 127.2, 126.5, 125.9, 123.2, 120.3, 71.2, 32.5, 25.9, 23.4, 18.1, 14.1. Anal. calcd for $C_{22}H_{22}O_3$: C, 79.02; H, 6.63. Found: C, 78.69; H, 6.77.

2.2.4. 2-(2′-Methyl-3′-butenyl)-1-hydroxy-9,10-anthraquinone **26**

1-(3′-Methyl-2′-butenyloxy)-9,10-anthraquinone **8** (2.88 g, 9.86 mmol) was dissolved into 125 mL 1-butanol, in a modification of the method of Murty et al. [13]. An addition funnel was charged with a solution of $NaHCO_3$ (3.31 g, 39.4 mmol) in 60 mL water. Argon was bubbled through both solutions for 2 h. The anthraquinone solution was warmed to reflux, and then D-glucose (8.88 g, 49.3 mmol) was added. The reaction mixture was allowed to stir at this temperature for 10 min. prior to the dropwise addition of the aqueous bicarbonate. Following the addition, the reaction was allowed to proceed for 35 min. and then quenched by addition of 25 mL of 1N HCl and 100 mL water. The aqueous layer was washed 2 × 100 mL portions of 1:1 ethyl acetate/CH_2Cl_2. The combined organic layers were dried with anhydrous $MgSO_4$, and concentrated in vacuo. The resulting solid was recrysallized from heptane to yield an orange powder (1.60 g, 5.48 mmol, 56%). mp 117.0–119.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (s, 6H), 5.08 (m, 2H), 6.28 (dd, J = 10.5, 17.6 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.79 (m, 3H), 8.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 182.5, 162.2, 146.3, 144.0, 134.5, 134.4, 134.1, 133.7, 133.6, 131.7, 127.2, 127.0, 119.1, 115.9, 111.5, 41.3, 26.7. Anal. calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.90; H, 5.50.

2.2.5. Anthraquinone dihydrofuran **39**

2-(1,1-Dimethylallyl)-1-hydroxy-9,10-anthraquinone **26** (50 mg, 0.17 mmol) was dissolved in 25 mL CH_2Cl_2. Methanesulfonic acid (4 mL) was added dropwise, causing the solution to change from bright yellow to dull brown. The reaction was followed by TLC (CH_2Cl_2) until consumption of **26** (R_f = 0.95) and accumulation of **39** (R_f = 0.6) were indicated. The solution was washed with saturated aqueous bicarbonate (3 × 30 mL), water (1 × 30 mL), and brine (1 × 30 mL). The organic layer was dried over $MgSO_4$ and conc. in vacuo to give a yellow solid. The solid was dissolved in minimal CH_2Cl_2 and eluted on a preparatory TLC plate. The band corresponding to **39** was visualized by UV and cut from the plate. The desired compound was washed from the silica by stirring in CH_2Cl_2 and filtering. Concentration of the filtrate gave **39** as a yellow powder (29 mg, 0.1 mmol, 59%). mp 98.5–100.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.39 (s, 3H), 1.52 (d, J = 6.6 Hz, 3H), 4.71 (q, J = 6.6 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.75 (m, 2H), 7.93 (d, J = 7.5 Hz, 1H), 8.29 (m, 2H). ^{13}C NMR (75 mHz, $CDCl_3$) δ 183.1, 182.3, 159.2, 147.2, 134.4, 134.0, 133.5, 133.3, 129.1, 127.7, 127.2, 127.0, 121.3, 116.8, 91.3, 43.1, 26.2, 23.1, 14.8. Anal. calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.95; H, 5.49.

2.3. Photochemical reactions

2.3.1. General photochemical method

All photochemical reactions were carried out in Pyrex glassware. Solutions were stirred by magnetic stirring throughout photolysis. The solutions were prepared and then degassed by three cycles of freeze-pump-thaw, followed by back filling the reaction vessel with dry Ar, unless otherwise indicated. The solutions were then irradiated with a 450 W medium pressure Hg lamp (Hanovia) encased in a uranium oxide doped glass filter (366 nm) or in a Rayonet reactor equipped with 16 lamps emitting at 419 nm.

*2.3.1.1. Anthraquinone acetal **10**.* 1-(3′-Methyl-2′-butenyloxy)-9,10-anthraquinone **8** (32 mg, 1.27×10^{-4} mol) was dissolved in a mixture of acetic acid (60 mL) and water (40 mL) and the solution degassed by three cycles of freeze-pump-thaw. The yellow solution was irradiated at 366 nm

for 16 h. Solvent was removed in vacuo and the residue subjected to preparatory scale TLC. The band corresponding to the product was cut from the plate and the product eluted from the silica by stirring in 50 mL $CHCl_3$ for 6 h. The mixture was filtered and concentrated in vacuo to give **10** as yellow crystals (16.0 mg, 6.4×10^{-5} mol, 50%). mp 156.0–158.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.47 (s, 3H), 4.06–4.09 (dd, J = 1.9, 7.9 Hz, 1H), 4.13–4.18 (dd, J = 1.9, 6.0 Hz, 1H), 4.58–4.61 (dd, J = 1.9, 6.0 Hz, 1H), 7.45–7.50 (t, J = 7.7 Hz, 1H), 7.55–7.62 (m, 2H), 7.69–7.75 (td, J = 1.3, 7.5 Hz, 1H), 7.98–8.00 (dd, J = 0.8, 7.7 Hz, 1H), 8.04–8.07 (dd, J = 1.3, 7.5 Hz, 1H), 8.23–8.26 (dd, J = 1.1, 7.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.4, 141.1, 137.3, 135.8, 133.8, 132.3, 131.3, 130.0, 129.2, 128.9, 127.1, 126.1, 125.4, 98.1, 83.5, 65.1, 38.9, 31.1, 23.4. Anal. calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.72; H, 5.52.

*2.3.1.2. Anthraquinone dihydropyranyl alcohol **11***. 1-(3′-Methyl-2′-butenyloxy)-9,10-anthraquinone **8** (3.00 g, 10.3 mmol) was dissolved in 2145 mL acetic acid and 1755 mL distilled water. Argon was bubbled through the solution for 3 h to remove dissolved oxygen. The solution was then irradiated at 366 nm for 16 h. The resulting solution was diluted with water and extracted extensively with chloroform. The organic layers were washed with water and aqueous bicarbonate, and concentrated in vacuo. The crude product was a greenish brown oil. The product was purified using flash column chromatography with an ethyl acetate/hexane mobile phase, starting at 15% ethyl acetate, increasing to 80% ethyl acetate. Products eluted in the order: 1-hydroxy-9,10-anthraquinone **6**, anthraquinone acetal **10**, and pyran alcohol **11**. The chromatographed products were recrystallized separately from THF and hexanes to give 1-hydroxy-9,10-anthraquinone **6** (880 mg, 3.9 mmol, 38%), anthraquinone acetal **10** (860 mg, 2.9 mmol, 29%), and yellow–orange crystals of **11** (380 mg, 1.2 mmol, 11%). Data for **11**: mp 205.0–206.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6) δ 1.36 (s, 3H), 1.37 (s, 3H), 3.76 (m, 1H), 4.23 (dd, 1 H, J = 11.3, 6.2 Hz), 4.40 (dd, 1 H, J = 11.3, 3 Hz), 5.29 (d, 1 H, J = 4.2 Hz), 7.82 (m, 4H), 8.05 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$/DMSO-d_6) δ 188.7, 187.0, 152.0, 136.6, 135.4, 134.3, 133.4, 133.3, 132.7, 127.5, 126.7, 124.4, 121.2, 120.3, 71.0, 67.7, 37.2, 30.1, 25.0. HRMS calcd for $C_{19}H_{16}O_4Na^+$: 331.09408. Found: 331.09318.

*2.3.1.3. Photolysis of 1-allyloxy-9,10-anthraquinone **18***. 1-Allyloxy-9,10-anthraquinone [14], **18** (24.0 mg, 9.1×10^{-5} mol) was dissolved in a mixture of distilled water (40 mL) and acetic acid (60 mL). The yellow solution was degassed by three cycles of freeze-pump-thaw and irradiated at 366 nm for 24 h. The solution was partitioned between $CHCl_3$ and water. The aqueous layer was extracted further with $CHCl_3$ (3×75 mL). The combined organic layers were conc. in vacuo. The residue was chromatographed using preparative scale TLC (one elution with $CHCl_3$) and the band corresponding to 1-hydroxy-9,10-anthraquinone **6** was cut from the plate. The product was eluted from the silica by vigorous stirring in $CHCl_3$ for 6 h. The silica was removed by filtration and the filtrate conc. in vacuo to give **6** (18.4 mg, 8.2×10^{-5} mol, 90%).

*2.3.1.4. Preparation of 4-hydroxy-2-nonenal from **20***. In 9:1 MeOH:H_2O (25 mL) **20** (100 mg, 0.246 mmol) was dissolved in a 50 mL round bottom flask. A septum was attached to the flask with an O_2 balloon via a needle. The sample was irradiated at 366 nm while being stirred vigorously. After 3 h, the sample was conc. in vacuo to near dryness. An additional 10 mL of distilled water was added, and the flask was again conc. in vacuo. The aqueous layer was pipetted out; the orange-yellow solid was washed with distilled water (5 mL) and dried in vacuo. The aqueous layers containing 4-HNE were combined with brine, extracted with $CHCl_3$ (5×30 mL) and conc. in vacuo to give 4-HNE as a pale yellow oil (35.0 mg, 91%).

*2.3.1.5. Photochemical preparation of **22** from **20***. In MeOH (25 mL) **20** (101.0 mg, 0.25 mmol) was dissolved. The resulting yellow solution was degassed via three cycles of freeze-pump-thaw and then irradiated at 419 nm while being stirred vigorously. After 5 h, the sample was conc. in vacuo. The resulting orange-yellow solid was stirred in 10 mL distilled water for 1 h. The liquid was removed via pipet and the residue stirred again in 10 mL distilled water. This was repeated three times. The solid residue was dried in vacuo. The aqueous layers were combined, washed with brine, and extracted with $CHCl_3$ (5×40 mL). The crude mixture was then chromatographed on silica (4:1 hexanes:EtOAc) to give **22** as a pale orange solid (46.8 mg, 42%), 4-HNE (11.6, 30%) and **21** (21.1 mg, 32%). Data for **22**: IR (NaCl, cm^{-1}) 3428, 3019, 2962, 2932, 1671. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91–0.98 (m, 6H), 1.25–1.65 (m, 11H), 2.56–2.71 (m, 2H), 3.02 (s, 3H) 4.30–4.35 (m, 1H), 6.04–6.11 (m, 1H), 6.17 (d, J = 4.7 Hz, 1H), 6.23–6.30 (dd, J = 15.6, 5.5 Hz, 1H), 7.24–7.26 (m, 1H), 7.49–7.62 (m, 3H), 7.80–7.85 (m, 1H), 8.12–8.15 (dd, J = 7.4, 1.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.7, 148.8, 139.0, 137.4, 135.8, 133.0, 131.5, 130.3,130.0, 129.3, 127.7, 125.00, 124.99, 122.9, 119.6, 92.14, 92.11, 71.8, 49.3, 37.0, 31.8, 31.7, 29.3, 25.0, 22.6, 22.5, 14.0. HRMS calcd for $C_{26}H_{32}O_5Na^+$:459.21203. Found: 459.21647.

*2.3.1.6. Photolysis of **23***. In 79% aqueous acetic acid (24 mL) was dissolved 1-(3′-methyl-2′-butenyl)oxy-2-propyl-9,10-anthraquinone, **23** (50.5 mg, 0.15 mmol). The resulting yellow solution was degassed by three cycles of freeze-pump-thaw and then irradiated at 366 nm for 3.6 h. The acetic acid was quenched with saturated $NaHCO_3$, and the product was extracted with EtOAc (3×50 mL). The organic layers were combined and concentrated in vacuo to give 1-hydroxy-2-propyl-9,10-anthraquinone, **21** (40.0 mg, 100%).

*2.3.1.7. Anthraquinone dihydropyranyl acetate **27***. 2-(2′-Methyl-3′-butenyl)-1-hydroxy-9,10-anthraquinone **26** (77 mg, 2.64×10^{-4} mol) was dissolved in acetic acid (100 mL) and the solution degassed by three cycles of freeze-pump-thaw. The yellow solution was irradiated at 366 nm for 16 h. The mixture was poured into 500 mL of saturated aqueous $NaHCO_3$ and extracted (5×50 mL) $CHCl_3$. The combined organic layers were washed with aqueous $NaHCO_3$, water, brine and dried over anhydrous $MgSO_4$. Solvent was removed in vacuo and the residue subjected to preparatory scale TLC (first elution: $CHCl_3$; second elution: 5% acetone in $CHCl_3$). The band corresponding to the product fluoresced with a green color (characteristic of anthraquinone pyrans **11**, **27** and **28**) when irradiated with 366 nm light from a handheld lamp. In contrast, 1-hydroxy-9,10-anthraquinones (e.g. **6** or **26**) fluoresced with an orange color when similarly irradiated. The band corresponding to the product was cut from the plate and the product eluted from the silica by stirring in 50 mL $CHCl_3$ for 6 h. The mixture was filtered and concentrated in vacuo to give the product as yellow crystals (52.8 mg, 1.51×10^{-4} mol, 57%). mp 141.0–144.0. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 3H), 1.48 (s, 3H), 2.08 (s, 3H), 4.19 (dd, J = 5.1, 8.9 Hz, 1H), 4.81 (m, 2H), 7.62 (dd, J = 0.9, 7.8 Hz, 1H), 7.77 (m, 2H), 7.92 (dd, 1 H, J = 7.8 hz) 8.29 (m, 2H). ^{13}C NMR (75 mHz, $CDCl_3$) δ 182.9, 182.0, 170.3, 161.5, 136.6, 134.3, 134.2, 134.1, 133.6, 133.2, 131.1, 127.2, 127.0, 120.8, 116.9, 83.1, 75.1, 49.5, 31.6, 23.4, 22.7. HRMS calcd for $C_{21}H_{18}O_5Na^+$: 373.10464. Found: 373.10413.

*2.3.1.8. Anthraquinone dihydropyranyl methyl ether **28***. 2–(2′-Methyl-3′-butenyl)-1-hydroxy-9,10-anthraquinone **26** (22.1 mg, 7.57×10^{-5} mol) was dissolved in methanol (48 mL) and the solution degassed by three cycles of freeze-pump-thaw. The yellow solution was irradiated at 366 nm for 24 h. Solvent was removed in vacuo and the residue subjected to preparatory scale TLC. The band corresponding to the product (see procedure for **27**) was cut from the plate and the product eluted from the silica by stirring in 50 mL $CHCl_3$ for 6 h. The mixture was filtered and concentrated in vacuo to give the product as yellow crystals (18.3 mg, 5.68×10^{-5} mol, 75%). mp 84.0–86.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.16 (s, 3H), 3.29 (s, 3H), 3.68 (dd, J = 6.0, 8.7 Hz, 1H), 4.82 (m, 2H), 7.72 (m, 3H), 7.88 (d, J = 7.5 Hz), 8.29 (m, 2H). ^{13}C NMR (75 mHz, $CDCl_3$) δ 183.0, 182.1, 161.5, 137.7, 134.3, 134.1, 133.9, 133.5, 133.2, 131.6, 127.1, 126.9, 120.7, 116.6, 75.5, 49.9, 49.3, 29.7, 21.9, 21.1. Anal. calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.32; H, 5.59.

2.4. Radical trapping experiments

2-(1,1-Dimethylallyl)-1-hydroxy-9,10-anthraquinone **26** (29.3 mg, 0.1 mmol) was stirred in methanol (30 mL) with thiophenol (2, 5, or 10 equiv.). The solution was degassed by three cycles of freeze-pump-thaw. The pale yellow solution was then irradiated at 366 nm for 16 h, at the end of which it had turned orange. The solution was diluted with ethyl acetate and washed with water and aqueous bicarbonate. The organic layer was then dried over magnesium sulfate and concentrated in vacuo. The crude products were then analyzed by ^{1}H NMR and GC-MS.

Using 2 equivalents of thiophenol (relative to **26**), the ratio of **39** to **28** was 1.4:1. Using 5 equivalents of thiophenol the ratio was 4:1 and with 10 equivalents of thiophenol, the ratio was >7:1. In the experiment using 10 equivalents of thiophenol, the crude mixture was purified by flash column chromatography (50% ethyl acetate/hexane eluent). The recovery of **39** was 16.9 mg (0.058 mmol, 77%) and that of **28** was 2.6 mg (0.008 mmol, 10%).

3. Results and discussion

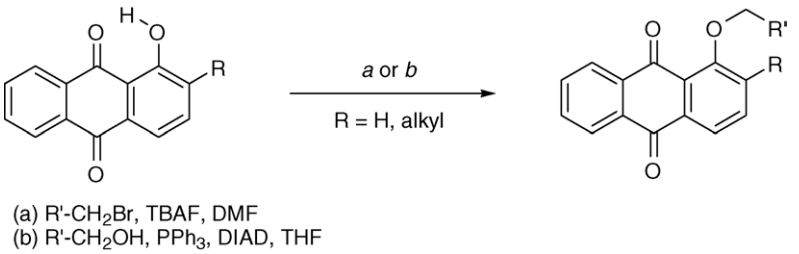
*3.1. Photochemistry of 1-(3,3-dimethyl-2-propenyloxy)-9,10-anthraquinone **8***

Anthraquinone **8** was prepared in 95% yield by alkylation of **6** with 3-methyl-2-butenyl alcohol under Mitsunobu conditions (Scheme 2, R=H). In general, 1-hydroxy-9,10-anthraquinones could be alkylated either by treatment with an alkyl bromide in the presence of TBAF in DMF (Scheme 2a) or under Mitsunobu conditions (Scheme 2b). Both methods are effective and the choice of which to use is best made based on the availability of the required bromide or alcohol.

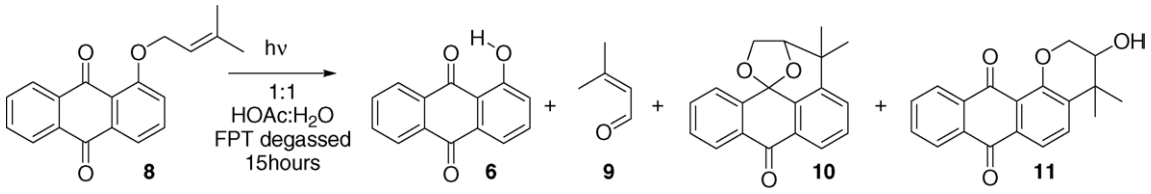
Irradiation of **8** in oxygen saturated methanol did indeed produce the expected **6** (76% yield) and aldehyde **9**, though it was difficult to accurately measure the yield of the volatile aldehyde. However, the yield of **6** and **9** was not as high as expected and a number of anomalous signals were observed in the ^{1}H NMR spectrum of the reaction.

Speculating that slow hydrolysis of the acetal (e.g. **4** or **5**) lowered yields, we attempted the reaction in oxygenated 1:1 acetic acid:water. These conditions gave fairly clean conversion to **6**, aldehyde **9**, and one other product (**10**) produced in a 2:2:1 ratio, as determined by NMR (Scheme 3). When oxygen was excluded, the same products were obtained, but the yield of **10** rose to 50%. NMR experiments suggested the structure shown for **10**. The compound was recrystallized, and an X-ray structure (Fig. 1) confirmed this structure. Upon scale-up of the reaction, a second unexpected product (**11**) was isolated in 11% yield. This compound was also crystallized and its structure confirmed by X-ray crystallography (Fig. 2).

The conversion of **8** to **10** was remarkable. An aryl C–O bond was broken and an aryl C–C bond formed in its place. Furthermore, following the rearrangement that led to the new C–C bond, the allyloxy remnant added across the quinone carbonyl, producing an unusual anthraquinone acetal that survived exposure to the aqueous acidic environment. This reaction was also very sensitive to the presence of oxygen; when the reaction was run in less rigorously degassed solution (for example, on a larger scale with bubbling argon used in place



Scheme 2. General methods for alkylation of 1-hydroxy-9,10-anthraquinones.



Scheme 3. Anaerobic photolysis of 8.

of freeze-pump-thaw), the yield of **10** fell off rapidly. The reaction was also solvent dependent. Aqueous acetic acid was the optimum solvent, but **10** was also observed when the photolysis was carried out in polar solvents such as alcohols or DMF, although yields with these solvents are lower. Photolysis in non-polar solvents such as benzene gave no **10** and slow conversion to **6**.

Given the dependence of the yield of **10** on acidic and anaerobic conditions, we believe reversible formation of **13** is responsible for this unexpected reaction (Scheme 4). Formation of **12** from **8** happened in the usual manner (Scheme 1) [6,7]. The cation (**12**) can be trapped by solvent to give **13** but, in the absence of oxygen, hydrolysis of **13** to **14** and aldehyde **9** was slow [15]. Under the reaction conditions, **13** can easily revert to cation **12**. In addition to trapping by solvent, cation **12** can be trapped by the electron rich aromatic ring to give spirocycle **15**. It is at this key point that the new C–C bond is formed. Elimination of an enol led to anthraquinone **16**. Nucleophilic attack of the enol oxygen on the quinone carbonyl provided intermediate **17**, which could give **10** by acid-catalyzed addition of the alcohol to the alkene. This mechanism accounts for the new C–C bond and for the relationship between oxygen concentration and yield of **10**.

Note that the intermediate cation (**12**) is further stabilized, relative to previous examples in the literature [6,7], by conjugation with the electron-rich alkene. The increased stability of the cation should slow its reaction with solvent and shift the equilibrium towards **12**, relative to a simple alkoxy group. The cyclization of **12** to **15** is also likely accelerated by the *geminal* dimethyls [16–18]. An analogue lacking the

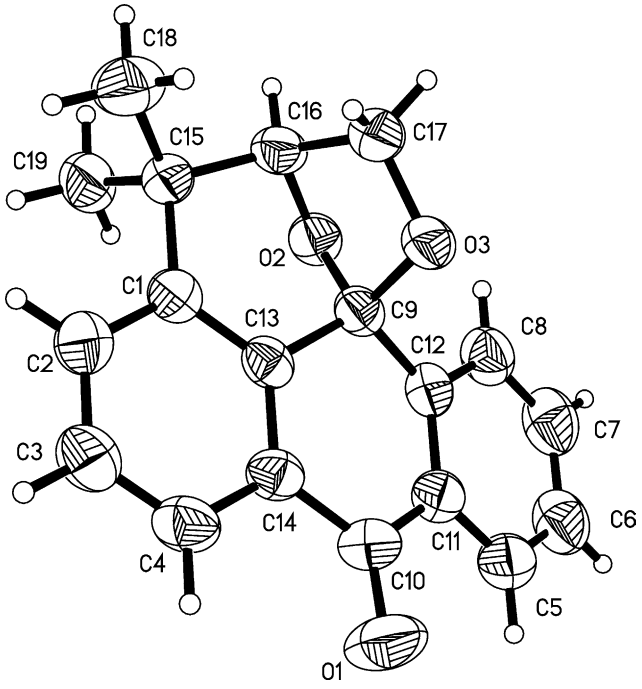


Fig. 1. X-ray structure of 10.

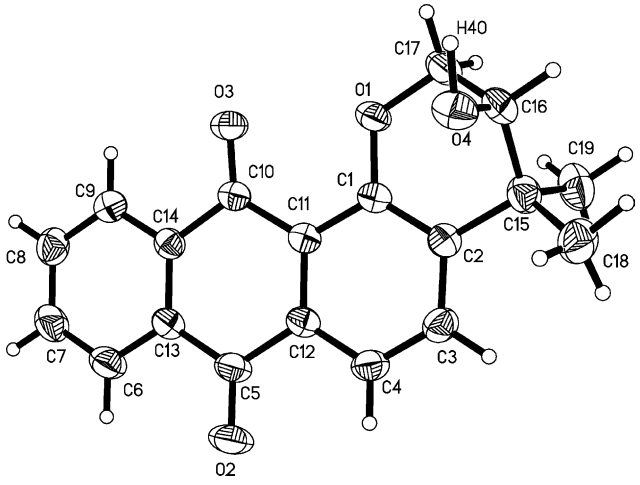
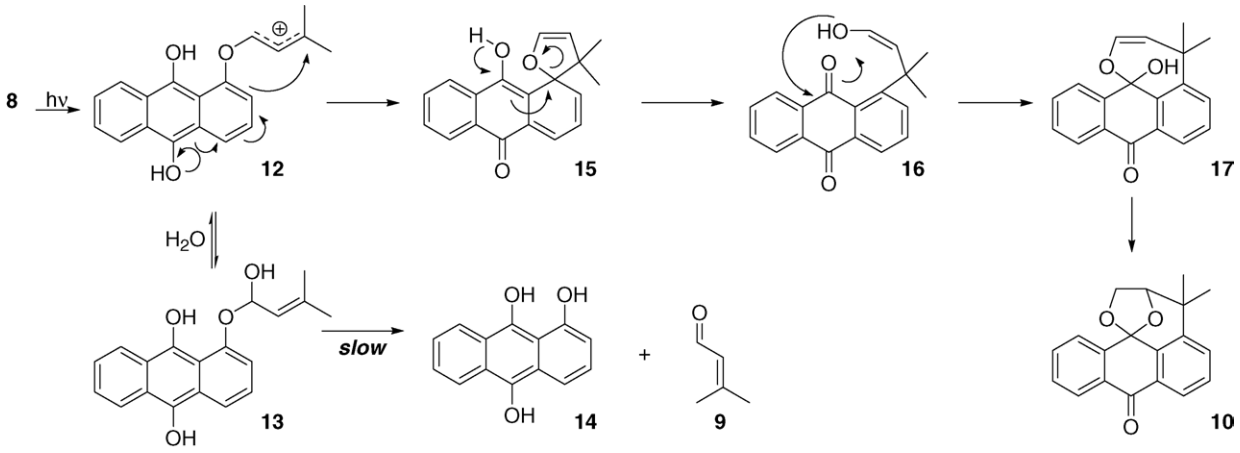
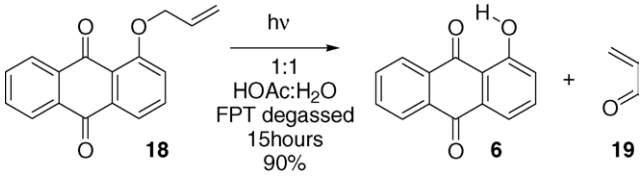


Fig. 2. X-ray structure of 11.



Scheme 4. *Proposed* mechanism for the formation of 10 from 8.



Scheme 5. Photolysis of 1-allyloxy-9,10-anthraquinone 18.

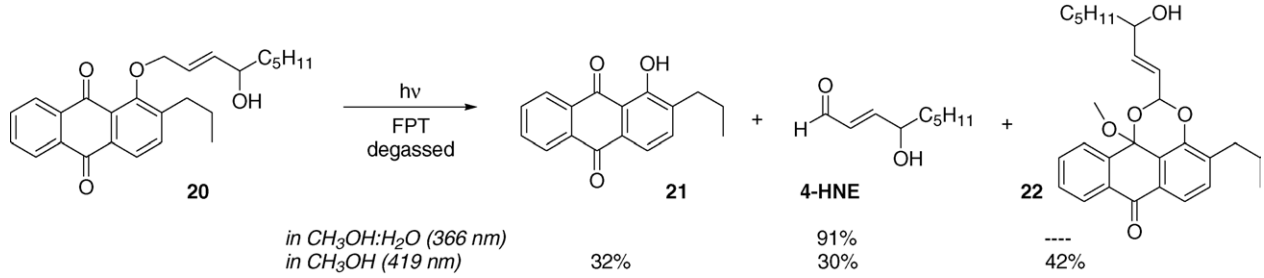
dimethyl substituents, 1-allyloxy-9,10-anthraquinone **18**, did not give any **10**-like product, instead producing **6** in 90% yield when irradiated in degassed aqueous acetic acid (Scheme 5).

An intermediate example, between **18** and **8**, is caged 4-hydroxynonenal (4-HNE) **20**. Anthraquinone **20** was designed to release the bioactive aldehyde 4-HNE when irradiated [5]. It served this purpose well under either aerobic or anaerobic conditions. In aerobic, aqueous methanol, 4-HNE was isolated in 91% yield following photolysis of **20** at 366 nm for 2 h. However, we also found that an unexpected acetal (**22**) was formed when the photolysis was carried out anaerobically at 419 nm (Scheme 6). Photolysis of **20** in anaerobic, anhydrous methanol at 419 nm gave **22** in 42% yield. **22** was converted to 4-HNE and **21** either upon treatment with acid or photolysis at 366 nm. We found no products corresponding to the formation of **10** from **8** in the photochemistry of **20**. Most likely the 2-propyl group accelerated the expected reaction (aldehyde production) relative to the formation of **10**-like products by keeping the allyl group oriented toward the proximal quinone oxygen [6,7]. This effect was also observed in the photochemistry of **23** (Scheme 7). Irradiation of **23** in anaerobic aqueous acetic acid gave a quantitative yield of **21** and **24**, with no **10**-like products observed. It is clear that the fate of the zwitterion formed in photolysis of 1-*allyl*oxy-9,10-anthraquinones lacking a 2-substituent was not as straightforward as that in the 1-alkoxy-9,10-anthraquinones reported previously [6–9].

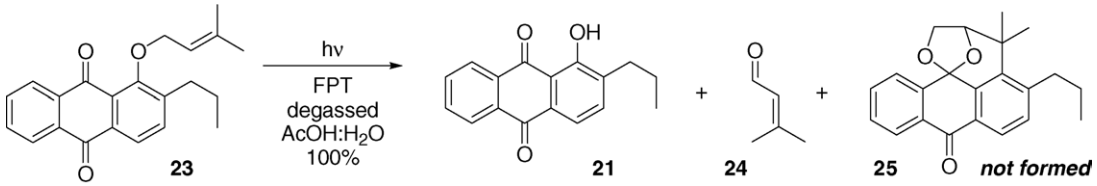
3.2. Photochemistry of 2-(1,1-dimethyl-2-propenyl)-1-hydroxy-9,10-anthraquinone *26*

The formation of **11** was reminiscent of the photocyclization product of *o*-allyl naphthols reported by Chow et al. [19]. However, the pyran ring in **11** was left in a higher oxidation state than those in Chow's work and was, therefore, unlikely to form from a simple photochemical acid/base reaction. An analogous pathway leading to **11** would require **26** to be produced on the path from **8** to **11**. **26** can be obtained from **8** via a Claisen rearrangement. Thus, we speculated that a Claisen rearrangement must occur during photolysis of **8** and the product of this rearrangment undergo photocyclization to give **11**. We confirmed this hypothesis by photolysis of **26** prepared independently (Scheme 8).

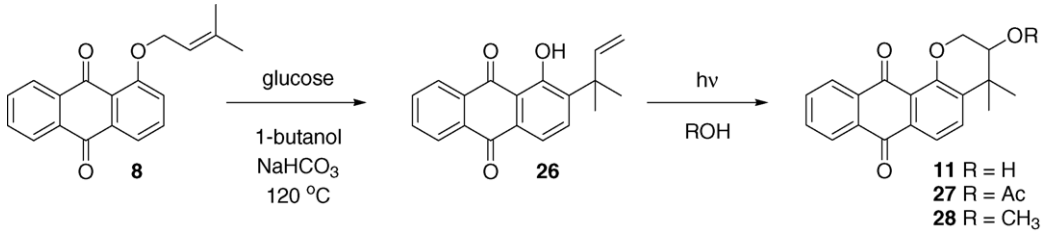
Irradiation of **26** in degassed aqueous acetic acid under the same conditions as for **8** gave **11** in 30% yield, along



Scheme 6. Photolysis of caged 4-hydroxynonenal **20**.



Scheme 7. Photolysis of 2-propyl-1-prenyloxy-9,10-anthraquinone **23**.



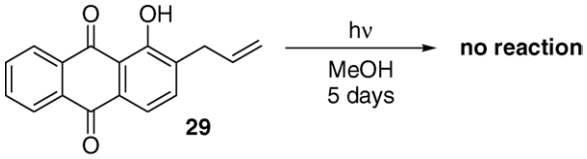
Scheme 8. Independent preparation of Claisen product **26**.

with a 55% yield of the corresponding acetate **27**. Irradiation of **26** in degassed acetic acid alone or methanol provided the acetate **27** or methyl ether **28** in 57% and 75% yields, respectively. Thus, the photocyclization reaction of the **26** was quite efficient. In this case, too, the geminal dimethyls are crucial. When 1-hydroxy-2-allyl-9,10-anthraquinone **29** [14], was irradiated under identical conditions for 5 days, no reaction occurred (Scheme 9).

Though the formation of substituted pyrans was efficient when **26** was irradiated, when **8** was irradiated, products resulting from **26** were low, indicating that the Claisen rearrangment during the course of photolysis of **8** was a minor pathway. Why a Claisen rearrangement should occur at all in the photolysis of **8** was not entirely clear.

3.3. Claisen rearrangments during the photolysis of 8

Clearly **26** must be produced during the anaerobic photolysis of **8**. The formation of **26** was unlikely to be the result of a typical photo-Claisen rearrangment, as none of the other expected reaction products were observed [20]. Thermal Claisen rearrangements of 1-allyloxy-9,10-anthraquinones, including **8**, occur only at high temperature or under reductive conditions [21]. The temperature of the photolysis reactions described above never exceeded 30 °C. However, a photoreduction of **8** was plausible and would permit the Claisen rearrangement to occur at much lower temperatures. In the absence of added reducing agent, we surmised that hydroanthraquinone **30** could serve as the reductant



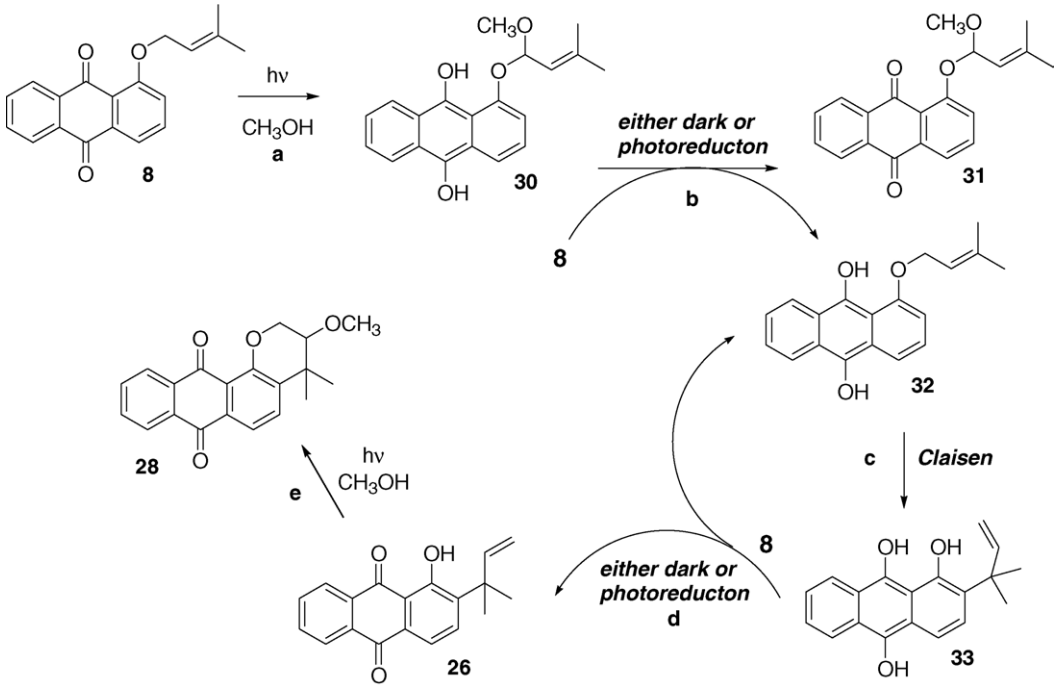
Scheme 9. Photolysis of 1-hydroxy-2-allyl-9,10-anthraquinone **29**.

in this photoreduction. Under the anaerobic conditions, anthrahydroquinone acetal **30**, produced by the photolysis of **8** (Scheme 4), should survive in solution long enough to reduce unreacted **8** [15]. This could be either a dark or photoreduction.

Scheme 10 shows our account of how Claisen product **26** was produced during the course of photolysis of **8**. Anthraquinone **8** was converted to acetal **30** (Scheme 10a) as described in Section 1. Under the anaerobic conditions, the acetal was relatively stable to hydrolysis [6] and survived long enough to reduce another molecule of **8** (Scheme 10b), producing anthraquinone **31** (which quickly hydrolyzed) and hydroanthraquinone **32**. The latter (**32**) was susceptible to Claisen rearrangement (Scheme 10c), which gave **33**. The cycle can continue with hydroanthraquinone **33** reducing **8**, while being oxidized to **26** (Scheme 10d). Anthraquinone **26** then underwent the oxidative photocyclization (Scheme 10e), while **32** underwent a Claisen rearrangement (Scheme 10c). This model predicts that the extent of Claisen rearrangement during photolysis of **8** should be dependent on the concentration of **8**. This was indeed what we found; when 10 mM **8** was irradiated in degassed methanol, **26** was detected after 2 h (by GC). When the concentration of **8** was 1 mM, no **26** (or pyran **28**) was detected at the same time point.

3.4. Mechanism of the oxidative photocyclization

From **26**, photoinduced abstraction of the phenolic hydrogen by the proximal carbonyl oxygen would then give an oxyradical **34**, that could add to the alkene in 6-*endo* fashion to produce carbon centered radical **35** (Scheme 11). Intramolecular electron transfer from the secondary carbon radical to the semiquinone radical in **35** would produce zwitterion **36**, which could be trapped by solvent to provide anthrahydroquinone **37**. The route from **35** → **36** → **37** is exactly analogous to that for **2** → **3** → **4** shown in Scheme 1. Oxidation of **37** upon exposure to air would give the product

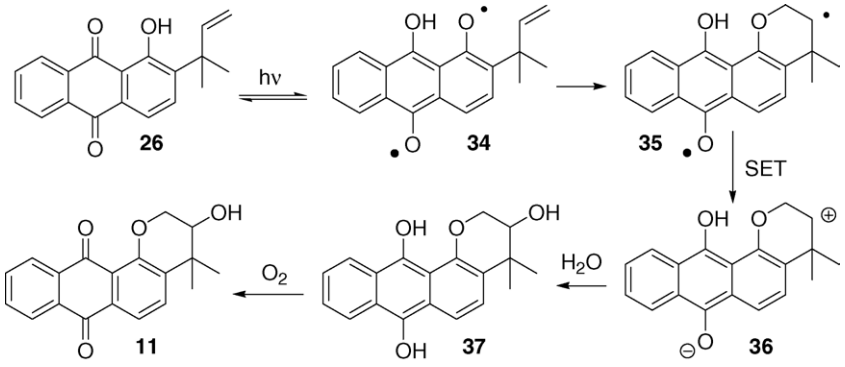


Scheme 10. Reduction of **8** by hydroanthraquinone **30**.

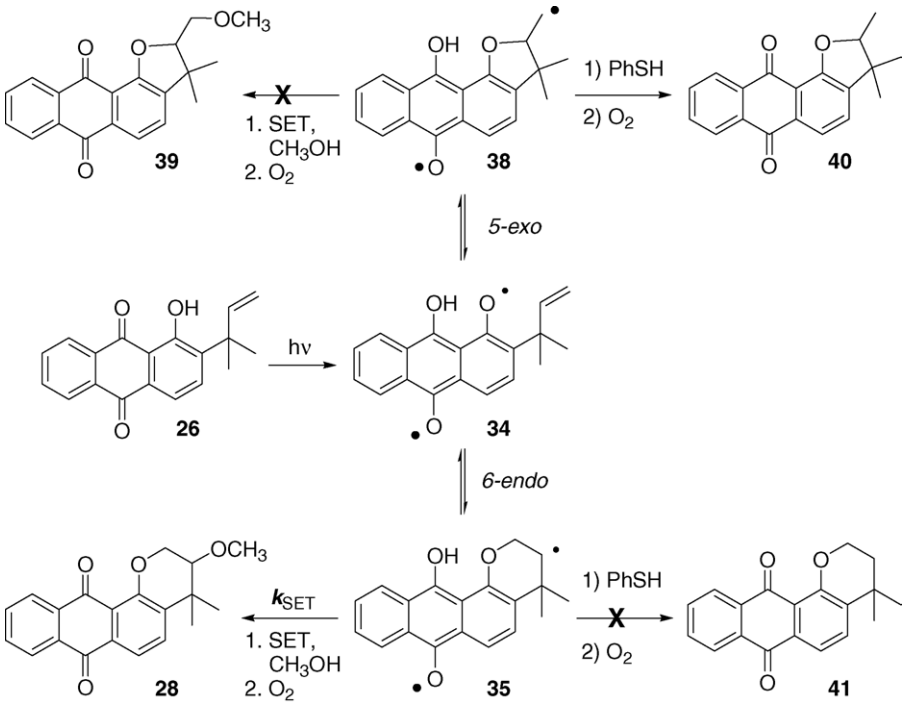
pyran. That photolysis of **26** led to **11** was confirmed by the independent preparation of **26** (see Section 3.2).

The mechanism proposed to account for **11** clarifies why 6-*endo* cyclization is observed (Scheme 12). Oxidation of primary radical **38** should be very slow. Given the nature of the phenolic radical **34**, we concluded that both the 5-*exo* and 6-*endo* cyclizations were reversible. To confirm that pyrans **11**, **27** and **28** were the product of a radical cyclization, the photolysis of **26** was carried out in the presence of thiophenol and methanol. Under these conditions, furan **40** was the major product but the ratio of **40** to other products was dependent on thiophenol concentration. Pyran **28** was obtained as a minor product even when 10 equivalents of thiophenol were used. No pyran **41** or furanyl ether **39** were observed (by NMR) under any conditions. The ratio of **40** to **28** produced when **26** was irradiated in the presence of 10 equivalents of thiophenol was 10:1 as measured by NMR (77% and 10% isolated yields, respectively). This ratio fell to 1.4:1 when only 2 equivalents of thiophenol were used. In the absence of thiophenol, no furan **40** was observed, suggesting that the ring opening of **38** was faster than intramolecular SET in this diradical.

These results confirm that **28** and related pyrans were obtained through cyclization of a phenolic radical on the tethered alkene, followed by SET from the secondary radical to the semiquinone radical. Using a value of $4.1 \times 10^9\ M^{-1}\ s^{-1}$ for the rate constant of hydrogen abstraction from thiophenol by a 2° carbon radical, the data presented above allow the determination of a lower limit for the rate constant for electron transfer [22]. Our observations placed a lower limit on k_{SET} (for **35** to **36**) at $7 \times 10^7\ s^{-1}$. This value was consistent with measurements by Blankespoor and co-workers, which gave a k_{SET} for **2** to **3** of $2 \times 10^9\ s^{-1}$ [7].



Scheme 11. Mechanism for formation of Pyran **11**.



Scheme 12. Trapping of radical intermediates in the photolysis of **26**.

4. Conclusions

Two new photoreactions of anthraquinones have been observed. The photochemistry of 1-(3-methyl-2-butenyloxy)-9,10-anthraquinone **8** differs considerably from analogs that lack the allyl substituent. While the expected oxidative photodealkylation reaction described by Blankespoor occurs, the presence of the allyl fragment creates pathways leading to several rearrangments. One of these rearrangements occurs in moderate yield to produce a new C–C bond in place of the aryl C–O bond. The preparation of this structural motif is not trivial using other methods. The second pathway proceeds through a Claisen reaction and subsequent radical cyclization, which produces a 1,2-fused pyran ring on the anthraquinone. The radical cyclization occurs in high yield when carried out with the independently prepared Claisen product. We continue to investigate these new photoreactions, as well as the application of anthraquinone photochemistry to the photoactivation of bioactive aldehydes, such as *trans*-4-hydroxy-2-nonenal, which was produced in up to 91% yield using related photochemistry.

Acknowledgements

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