Sensitized Photooxidation of Ortho-Prenyl Phenol: Biomimetic Dihydrobenzofuran Synthesis and Total $^{1}$O$_2$ Quenching

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ABSTRACT

The sensitized photooxidation of ortho-prenyl phenol is described with evidence that solvent aproticity favors the formation of a dihydrobenzofuran [2-(prop-1-en-2-yl)-2,3-dihydrobenzofuran], a moiety commonly found in natural products. Benzene solvent increased the total quenching rate constant ($k_T$) of singlet oxygen with prenyl phenol by ~10-fold compared to methanol. A mechanism is proposed with preferential addition of singlet oxygen to prenyl site due to hydrogen bonding with the phenol OH group, which causes a divergence away from the singlet oxygen ‘ene’ reaction toward the dihydrobenzofuran as the major product. The reaction is a mixed photooxidized system since an epoxide arises by a type I sensitized photooxidation.

INTRODUCTION

Strategies to synthesize 2,3-dihydrobenzofuran natural products have attracted attention (1–8). One strategy was the cyclization of a prenylated phenol, ($\mathcal{E}$)-4-(2-hydroxyphenyl)-2-methyl-2-butenyl methyl carbonate 1 to reach dihydrobenzofuran ($\mathcal{R}$)-2 (Fig. 1) (9). Dihydrobenzofuran ($\mathcal{R}$)-2 is related to important biologically active natural products, including tremetone ($\mathcal{R}$)-3 from the herb white snakeroot (Ageratina altissima) (10–13), and new strategies to reach them are needed.

Visible-light strategies to synthesize dihydrobenzo furans include successful photoredox reactions of ortho-quinone methides (14) and [3 + 2] cycloadditions of phenols and styrenes (15). Visible-light strategies also include sensitized photooxidation, that upon irradiation of a sensitizer, singlet oxygen ($^{1}\text{O}_2$) is efficiently produced (type II reaction), as well as amounts of oxygen radicals (type I) (16–18). Reports described sensitized photooxidation which gave dihydrobenzofurans, including literature examples of (−)-aductin E (19) and dehydroisoeugenol (20). We hypothesized that the sensitized photooxidation of ortho-prenyl phenol (4) will form a dihydrobenzofuran and that mechanistic insight will enable path manipulation to it, which is the subject of this paper.

Our work sought to elucidate mechanistic details on three fronts: whether (1) sensitized-photooxidation of prenyl phenol 4 leads to dihydrobenzofuran and allylic hydroperoxides, (2) solvent effects and competition exists between type I (oxygen radicals and ions) and type II ($^{1}\text{O}_2$) processes (16,17), and (3) total quenching rate constant ($k_T$) data of $^{1}\text{O}_2$ can yield new insight. The results provide evidence for the mechanism shown in Fig. 2, which reveals solvent aproticity increasing the reactivity of $^{1}\text{O}_2$ with the prenyl group in 4 and thus formation of dihydrobenzofuran.

MATERIALS AND METHODS

General. Benzaldehyde, DABCO, 3,3-dimethylallyl bromide, 4-methylphenoxacybenzoic acid (MCPBA, 77% purity with m-chlorobenzoic acid as the impurity), 2-methyl-2-pentene, NaH, NaHCO$_3$, NaNO$_2$, Na$_2$SO$_4$, and phenol were purchased from Sigma-Aldrich and used as received. Aluminum (III) phthalocyanine chloride tetrasulfonic acid (AlPcS$_4$) and tetraphenylporphyrin (TPP) were purchased from Frontier Scientific and used as received. Diethyl ether, ethyl acetate, hexanes, H$_2$O$_2$ (3 w/v%), pyridine, toluene (anhydrous), CHCl$_3$, CDCl$_3$, CD$_2$Cl$_2$, CD$_3$CN, C$_6$H$_6$, and C$_6$D$_6$ were purchased from VWR and used as received. Previously reported syntheses were used for prenyl phenol 4 (21) and 8-acetoxyethyl-2,6-dimethoxy-1,3,5,7-tetramethyl pyromethene fluoroborate (Br$_2$B-OAc) (22). Epoxide 8 was synthesized in 24.0 ± 2.2% yield by the reaction prenyl phenol 4 (1.54 mmol) with MCPBA (1.92 mmol) in 3.3 mL CHCl$_3$ at 0°C, which was followed by washing with 10% NaHCO$_3$, drying over Na$_2$SO$_4$, solvent removal, and silica gel column chromatography with hexanes/ethyl acetate (8:2).

Photooxidation reactions. Photooxidations of prenyl phenol 4 (0.10 mmol) were carried out in O$_2$-saturated C$_6$D$_6$ with TPP (0.1 mm) and in some cases DABCO (2 or 10 mm) or CH$_3$OH with AlPcS$_4$ (0.1 mm). Solutions were pre-saturated with O$_2$ and the TPP or AlPcS$_4$ sensitizers irradiated with two 400-W metal halide lamps through a longpass ≥400-nm filter solution (1-cm 75 w/v% NaNO$_2$) at 26°C. Temperature increases were ≤3°C over the course of the photolysis. Following photolyses carried out in CH$_3$OH, solvent was evaporated and replaced with CDCl$_3$ for NMR analysis. Benzaldehyde was unreactive under the reaction conditions and therefore used as an NMR internal standard.

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2-(3-Methyl-2-butenyl)phenol 4. 1H NMR (400 MHz, CDCl3) δ 7.17–7.11 (2H, m), 6.89 (1H, td, \( J = 7.4, 1.2 \) Hz), 6.83 (1H, dd, \( J = 8.5, 1.2 \) Hz), 5.37–5.33 (1H, m), 5.14 (1H, s), 3.39 (1H, d, \( J = 7.2 \) Hz), 1.81 (6H, s).

2-(Prop-1-en-2-yl)-2,3-dihydrobenzofuran 2 is a known compound (9).

1H NMR (400 MHz, CDCl3): δ 7.14 (2H, d, \( J = 8.0 \) Hz), 6.91–6.87 (1H, m), 6.84–6.81 (1H, m), 5.10 (1H, t, \( J = 1.2 \) Hz), 5.02 (1H, d, \( J = 4.0 \) Hz), 4.97 (1H, d, \( J = 4.0 \) Hz), 3.35 (1H, d, \( J = 8.0 \) Hz), 3.27 (1H, d, \( J = 8.0 \) Hz), 1.80 (3H, s).

2-(2-Hydroperoxy-3-methylbut-3-en-1-yl)phenol 6. 1H NMR (400 MHz, C6D6): δ 11.43 (1H, s), 7.01–6.96 (2H, m), 6.83–6.79 (1H, m), 6.81 (1H, m), 6.52 (1H, d, \( J = 8.0 \) Hz), 5.01 (1H, d, \( J = 1.6 \) Hz), 5.00 (1H, d, \( J = 1.6 \) Hz), 4.80 (1H, t, \( J = 1.6 \) Hz), 3.31 (1H, d, \( J = 12 \) Hz), 3.27 (1H, d, \( J = 8.0 \) Hz), 1.56 (3H, s).

(E)-2-(3-Hydroperoxy-3-methylbut-1-en-1-yl)phenol 7. 1H NMR (400 MHz, C6D6): δ 9.60 (1H, s), 7.01–6.96 (1H, d, \( J = 8.0 \) Hz), 6.83–6.79 (1H, m), 6.81 (1H, m), 6.52 (1H, d, \( J = 8.0 \) Hz), 6.33 (2H, d, \( J = 16.0 \) Hz), 1.56 (3H, s), 1.52 (3H, s).

2-((3,3-Dimethyloxiran-2-yl)methyl)phenol 8 is a known compound (23). 1H NMR (400 MHz, C6D6): δ 7.08–7.06 (2H, m), 7.01–6.96 (2H, m), 2.87 (1H, d, \( J = 8.0 \) Hz), 2.84 (1H, d, \( J = 8.0 \) Hz), 2.74 (1H, t, \( J = 8.0 \) Hz), 1.55 (3H, s), 1.52 (3H, s).

H2O2. 1H NMR (400 MHz, C6D6) broad δ 9.16 ppm; 1H NMR (400 MHz, CD3CN) δ 9.77 ppm; 1H NMR (400 MHz, CDCl3) δ 9.57 ppm; values were consistent to those reported in literature (24, 25).

In C6D6, doping with commercial H2O2 and the addition of co-solvent CD3CN to solubilize was carried out to verify the NMR signal. In CH3OH, H2O2 was detected after solvent evaporation and replacement with CDCl3.

Total quenching rate constant determinations. The setup (26) used 532 nm light (10 mJ pulse−1) from an Nd:YAG Q-switched laser operating at 5 Hz. Br2B-OAc (2.6 μM) was used as the sensitizer in C6H6 or CH3OH solutions of prenyl phenol 4 at 26°C. A H10330A-45 (Hamamatsu Corp.) photomultiplier tube operating at −650 V was used to detect the 1O2 phosphorescence. The phosphorescence was monitored through a band-pass filter centered at 1270 nm (OD4 blocking, FWHM = 15 nm) and signals collected on a 600 MHz oscilloscope. Kinetic data were fitted with a monoeponential function shown in Eq. (1).

Figure 1. Synthesis of dihydrofuran (R)-2 with the structure of tremetone (R)-3 shown to the right.

Figure 2. Proposed mechanism in the sensitized photooxidation of prenyl phenol 4, including solvent and DABCO additive effects.
where $I$ is the final intensity, $I_0$ is the initial intensity, $t$ is the time, $A$ is the amplitude, and $\tau_x$ is the total quenching rate constants ($k_T$) were obtained by fitting the data plotted of $k_{obs}$ vs [prenyl phenol] with Eq. (2).

$$k_{obs} = k_d + (k_T)[\text{prenyl phenol}]$$  \hspace{1cm} (2)

where $k_{obs}$ is the observed $^1\text{O}_2$ quenching rate constant, $k_d$ is the rate constant of deactivation of $^1\text{O}_2$ by the solvent.

**RESULTS AND DISCUSSION**

**Product formation**

The sensitized photooxidation reaction of prenyl phenol 4 (taken to $\leq$30% conversion) led to products 2, and 6-8 according to NMR (Table 1). Attempts were not made to isolate the 2° and 3° allylic hydroperoxides 6 and 7 due to the anticipated instability to column chromatography; the proton NMR hydroperoxide and alkene signals are similar to those reported in literature (27). The stabilities of hydroperoxides vary, on detection of 6 and 7 by NMR their decomposition was not seen in the reaction mixture over several hours. The identity of epoxide 8 was verified by its independent synthesis from 4 with MCPBA. There was evidence for the formation of $\text{H}_2\text{O}_2$ in the reaction, but was not quantitated as we and others (24,25) have noted a broad proton NMR signals from 9.16-9.77 ppm depending on solvent. The solvent was also found to modify the product yields.

**Effect of solvent on product formation**

In $\text{C}_6\text{D}_6$, dihydrofuran 2 was the main product, along with epoxide 8, with only small amounts of allylic hydroperoxides 6 and 7. In CH$_3$OH, the amount of dihydrofuran 2 decreased and amounts of allylic hydroperoxides 6 and 7 increased, but the amount of epoxide 8 remained nearly constant. The ratio of dihydrofuran 2 to hydroperoxides 6 and 7 is ∼9:1 in $\text{C}_6\text{D}_6$ and ∼2:3 in CH$_3$OH. Thus, there is a ∼4-fold decrease in dihydrofuran 2 in CH$_3$OH compared to $\text{C}_6\text{D}_6$. The ratio of hydroperoxides 6:7 is not found to depend on $\text{C}_6\text{D}_6$ and CH$_3$OH solvent, wherein the ratio of 6:7 in either solvent is ∼0.9:1. In $\text{C}_6\text{D}_6$ and CH$_3$OH, the yield of epoxide 8 remained nearly constant, which led us to study the addition of the known $^1\text{O}_2$ quencher DABCO (28). The addition of DABCO in the sensitized photooxidation of prenyl phenol 4 led to an absence in the formation of 2, 6, and 7, however the amount of epoxide 8 formed was not affected pointing to its formation by a type I process. The probable type I contribution led us to measure the quenching rate constants with $^1\text{O}_2$ to directly assess the type II process.

**Effect of solvent on the total $^1\text{O}_2$ quenching rate constant**

Time-resolved singlet oxygen phosphorescence quenching studies provided insight to the solvent effects. The total quenching rate constant ($k_T$) of $^1\text{O}_2$ by prenyl phenol 4 was measured in $\text{C}_6\text{H}_6$ and CH$_3$OH by monitoring its phosphorescence quenching at 1270 nm (Table 2). Figure 3A,B shows the decay curves are first-order and the lifetime ($\tau_{1/2}$) diminishes with increasing concentration of prenyl phenol 4 in $\text{C}_6\text{H}_6$ and CH$_3$OH. The $k_T$ values were obtained from the linear fit of the $k_{obs}$ ($1/\tau_{1/2}$) vs [prenyl phenol] showing a $k_T$ value ∼10-fold greater in $\text{C}_6\text{H}_6$ than in CH$_3$OH (Fig. 4A,B). This enhancement contrasts to solvent effects in di- and trisubstituted alklenes in aprotic to protic solvents that usually vary ≤2-fold (29,30). This aprotic solvent enhancement provides us with implications on the reaction mechanism, as we will discuss next.

**Mechanism of photooxidation**

The above results are rationalized in the mechanism shown in Fig. 2, and as follows: An experimental result is that dihydrobenzofuran formation depends on whether benzene or methanol solvent is used. The interaction of $^1\text{O}_2$ with the prenyl phenol 4 in benzene (Fig. 2, path A) and in methanol (Fig. 2, path B) can account for the ∼10-fold greater total quenching $k_T$. Data over a wider solvent range to compare not only hydrogen bonding ability, but also polarity $\varepsilon_T$ (30) scales are presently not available. With the available data, dihydrobenzofuran formation is proposed to involve H-bond interaction of phenolic hydrogen with $^1\text{O}_2$, directing it to the C°10 site in 5. The formation of a peroxo intermediate seems plausible, but evidence has not been found with preliminary trapping experiments using triaryl phosphites. The $^1\text{O}_2$ ‘ene’ regioselectivity in formation of the 2° and 3° allylic hydroperoxides 6 and 7 (ratio of ∼1:1) did not depend on whether benzene or methanol was the solvent. This is consistent with the cis-effect rule of the reaction of $^1\text{O}_2$ with trisubstituted alklenes, in which the more alkyl substituted side of the double bond is more reactive (31). Previous reports have shown instances where H-abstraction from the exo methyl group in trisubstituted alklenes contribute only a minor 5–10% in the formation of the 2° allylic hydroperoxide. In the presence of DABCO, the reaction did not form 2, 6, and 7, however the epoxide 8 yield was unaffected pointing to a type I process in its formation (Fig. 2, path C). These studies were carried out with DABCO concentrations that were insufficient to quench the sensitizer excited states, however the results do not rule out the epoxide’s formation via a peroxo prenyl phenol intermediate in a self-oxidation process.

<table>
<thead>
<tr>
<th>Products</th>
<th>Aprotic ($\text{C}_6\text{D}_6$)$^{+1,1}$</th>
<th>Prootic (CH$_3$OH)$^{+1,8}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>20.0 ± 4.0</td>
<td>5.1 ± 0.7</td>
</tr>
<tr>
<td>6</td>
<td>0.95 ± 0.07</td>
<td>3.0 ± 0.7</td>
</tr>
<tr>
<td>7</td>
<td>1.0 ± 0.03</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>8</td>
<td>7.5 ± 2.2</td>
<td>6.7 ± 0.6</td>
</tr>
</tbody>
</table>

Table 1. Effects of solvent and DABCO additive on the product ratios in the photooxidation of prenyl phenol 4.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$k_T$ (m$^{-1}$ s$^{-1}$) $\times 10^5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{C}_6\text{H}_6$</td>
<td>1.29 ± 0.6</td>
</tr>
<tr>
<td>CH$_3$OH</td>
<td>0.12 ± 0.06</td>
</tr>
</tbody>
</table>

Table 2. Total quenching rate constant ($k_T$) measurements of $^1\text{O}_2$ with prenyl phenol 4.†

Data represent the mean ± SD of 6 points at each concentration measured.
CONCLUSION

An interesting result of this study is the increased dihydrobenzofuran formation, when the photooxidation of 4 was carried out in aprotic solvent. This result points to adduct formation which decomposes to more stable species, 2 and H$_2$O$_2$. Decreasing the proticity of the solvent increases the interaction of 1O$_2$ with the phenolic hydrogen increasing the yield of dihydrofuran from 20.0% in benzene compared to 5.1% in methanol. The $k_T$ value showed a ~10-fold enhancement in benzene compared to methanol. Reported differences in product formation have been seen in terms of synthesis and mechanistic studies (16–18,33–41).

We are currently exploring (i) heterogeneous systems aimed at amplifying the formation of dihydrobenzofurans; (ii) whether a self-trapping reaction with 4 arises by a peroxy intermediate in the $^4$1O$_2$ reaction; and (iii) whether dihydrobenzofuran 2 reacts further by $^4$1O$_2$ [2 + 4] cycloaddition to form endoperoxides by analogy to phenol and naphthalene-1,5-diol (juglone)–$^3$O$_2$ reactions to reach an endoperoxide (42).

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REFERENCES


