Hydroxylation of Nitrated Naphthalenes with KO\textsubscript{2}/Crown Ether

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Superoxide radical anion (O\textsubscript{2}\textsuperscript{-}), generated by KO\textsubscript{2}/crown ether, is effective for hydroxylation of nitronaphthalenes. When mono- and di-nitrated naphthalenes are treated with KO\textsubscript{2}/crown ether, hydroxylation results at the electron-deficient site caused by the electron withdrawing effect of the substituted nitro group. Kinetic experiments suggest that the hydroxylation proceeds by two different mechanisms dependent on the first one-electron reduction potential of nitronaphthalenes.

Key words superoxide; nitroarene; hydroxylation; nitronaphthalene

Studying the introduction of a hydroxyl group to aromatic compounds is important not only for the development of the methodology for organic synthesis,\textsuperscript{1} but also for the clarification of the oxidative metabolisms in both endogenous and exogenous aromatic hydrocarbons by monoxygenases, such as cytochrome p450 enzymes.\textsuperscript{2} The microsomal cytochrome p450-dependent hydroxylation of benzene is mediated by hydroxyl radicals formed in a Haber–Weiss reaction with hydrogen peroxide and superoxide radical anion (O\textsubscript{2}\textsuperscript{-}).\textsuperscript{3} Hydroxyl radical-generating systems, which mimic the activity of monoxygenase, have been developed as synthetic tools for hydroxylation.\textsuperscript{4} However, hydroxylation is limited to substituted benzene and a few other arenes. The reactivity of the hydroxyl radical is very low when an aromatic ring is substituted by an electron-withdrawing group, such as the nitro group.\textsuperscript{5} Among the active oxygen species formed in biological systems, O\textsubscript{2}\textsuperscript{-} is of interest because of its unique reactivity toward electron-deficient sites in organic compounds.\textsuperscript{6}

We recently reported that O\textsubscript{2}\textsuperscript{-} generated by KO\textsubscript{2}/18-crown-6 was effective for the oxidation of 1-nitropyrene and 3-nitrofluorantene, and that direct hydroxylation without the accompanying nitro replacement reaction was characteristic of O\textsubscript{2}\textsuperscript{-} oxidation.\textsuperscript{7} The objective of the present study is to investigate the possibility of KO\textsubscript{2}/crown ether as a synthetic tool for hydroxylation of mono- and dinitronaphthalenes and the mechanistic aspect of aromatic hydroxylation with O\textsubscript{2}\textsuperscript{-}.

Experimental

General 1H-NMR and 1H–1H correlation spectroscopy (1H–1H COSY) spectra were recorded on a Varian Gemini 300 and VXR-400S in deuterated chloroform with tetramethylsilane (TMS) as the internal standard. Chemical shifts (\delta, ppm) are expressed relative to TMS, and coupling constants (J value) in hertz (Hz). Chemical shift assignments of all synthetic chemicals were made by the combination of one-dimensional nuclear overhauser effect (1D NOE) and COSY spectra. Preparative high-performance liquid chromatography (HPLC) was conducted on a Shimadzu LC-4A HPLC instrument with a silica gel column (5 mm, 20 mm i.d. \times 300 mm length) obtained from Soken Chemical & Engineering Co. (Tokyo, Japan). Cyclic voltammetric measurements were made with a Bioanalytical Systems BAS-100B (IN, U.S.A.) electrochemical analyzer using platinum working and auxiliary electrodes and a saturated calomel electrode as the reference. Ultraviolet (UV) spectra were run on a Shimadzu UV-240 instrument.

Chemicals KO\textsubscript{2} and 1,3-dinitronaphthalene were obtained from Aldrich Chemical Co. (Milwaukee, WI, U.S.A.). Dicyclohexano-18-crown-6, dimethylformamide (DMF), dichloromethane, and benzene were from Wako Pure Chemical Industries (Osaka, Japan) and 1- and 2-nitronaphthalene and 1,5-dinitronaphthalene were from Tokyo Chemical Industry Co., Ltd., (Tokyo, Japan). The 1,6- and 1,7-dinitronaphthalene were synthesized according to the procedure of Ward and Hawkins.\textsuperscript{8}

Reaction of Nitronaphthalene with KO\textsubscript{2}/18-Crown-6 The general procedure for hydroxylation consisted of adding nitronaphthalene (3 mmol) in dry benzene (50 mL) to a solution of KO\textsubscript{2} (8 molar excess) and dicyclohexano-18-crown-6 (2 or 4 molar excess) in dry benzene (50 mL) in the dark. The consumption of the starting nitronaphthalenes and formation of hydroxylated products were monitored by HPLC. After suitable reaction times (0.5–4 h), the mixture was quenched by acidification. The identity of the products was confirmed by NMR and mass spectral data after acetylation and purification by silica gel column chromatography.

Reaction of 1-nitronaphthalene with KO\textsubscript{2}/18-Crown-6 is as follows. To a mixture of KO\textsubscript{2} (1.70 g, 24 mmol) and dicyclohexano-18-crown-6 (3,17 g, 12 mmol) in the solution (50 mL) of benzene and DMF (1:2) was added a solution (50 mL) of 1-nitronaphthalene (0.52 g, 3 mmol) in benzene and DMF (1:2). The mixture was stirred for 1.5 h at 25°C in the dark and then quenched with water, acidified with concentrated HCl to pH 5, and extracted with dichloromethane. The extract was washed, dried over Na\textsubscript{2}SO\textsubscript{4}, evaporated, and treated with acetic anhydride (5 mL) and pyridine (2.5 mL) for 10 h. After the mixture was concentrated in vacuo, the residue was column chromatographed on silica gel with 30% CH\textsubscript{2}Cl\textsubscript{2}–n-hexane 10% EtOAc–30% CH\textsubscript{2}Cl\textsubscript{2}–n-hexane to obtain a mixture of products. The crude products were redissolved in dichloromethane and purified by HPLC eluted with n-hexane, dichloromethane, and ethyl acetate (8:1:1) to obtain 4-acetoxy-1-nitronaphthalene (70.9%) and 3-acetoxy-1-nitronaphthalene (11.6%) in that order.
Table 1. Results from the Treatment of Mono- and Dinitrophthalenes with KO₂/Crown Ether

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate Epcl vs. S.C.E.(a)</th>
<th>Reaction conditions</th>
<th>KO/crown (eq)</th>
<th>Products(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NO₂ 8/4 Benzene/DMF(c) 1.5 h</td>
<td>1.0-1082 mV</td>
<td>7.70.9%</td>
<td>8.11.5%</td>
</tr>
<tr>
<td>2</td>
<td>NO₂ 8/4 Benzene/DMF(c) 4h</td>
<td>2.0-1096 mV</td>
<td>9.9.4%</td>
<td>10.39.8%</td>
</tr>
<tr>
<td>3</td>
<td>NO₂ 8/2 Benzene 1.5 h</td>
<td>3.0-760 mV</td>
<td>11.90.4%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NO₂ 8/2 Benzene 2h</td>
<td>4.0-950 mV</td>
<td>12.24.4%</td>
<td>13.59.7%</td>
</tr>
<tr>
<td>5</td>
<td>NO₂ 8/2 Benzene 0.5 h</td>
<td>5.0-910 mV</td>
<td>14.54.3%</td>
<td>15.13.6%</td>
</tr>
<tr>
<td>6</td>
<td>NO₂ 8/2 Benzene 2h</td>
<td>6.0-813 mV</td>
<td>16.53.3%</td>
<td>17.35.4%</td>
</tr>
</tbody>
</table>

(a) Epcl of nitrophthalenes were determined by cyclic voltammetry. All measurements were recorded in DMF solution in 0.1 mol dm⁻³ Et₄NClO₄ using platinum working and auxiliary electrodes and a saturated calomel electrode as a reference.
(b) Yields for the reaction by KO/18-crown-6 were obtained as acetylated derivatives.
(c) The ratio of benzene and DMF was 1:2.

Results and Discussion

Nitrophthalenes (1–6) were oxidized by KO₂/crown ether to afford several hydroxylated compounds. In case of the mononitrophthalenes (1, 2), the reaction was carried out in a mixture of benzene and DMF (1:2), because the reaction rate of mononitrophthalene was very slow in benzene. In contrast, dinitrophthalenes (3, 4, 5, 6) were readily oxidized in benzene. The results are shown in Table 1. Throughout all reactions, it was clearly observed that KO₂/crown ether effectively reacted with the mono- and dinitrophthalenes, and hydroxylation preferentially proceeded at the p-position to the nitro substituents. No such oxidation was observed when the reaction was carried out in the absence of crown ether (data not shown), suggesting that O₂⁻ generated from KO₂/crown ether is responsible for the oxidation of nitrated naphthalenes. In the case of 2-nitrophthalene 2, which lacks the p-position, the reaction was slow and nucleophilic displacement of the nitro group by O₂⁻ occurred. Replacement of the nitro group during the reaction of 1,5-dinitrophthalene 4 in high yield is presumably the result of decreased hydroxylation at the 4-position due to the steric effect (peri strain) of the nitro group at the 5-position. Although both 1,6- and 1,7-dinitrophthalenes have an α- and β-nitro group in each benzene ring, 1,6-dinitrophthalene 5 has strong electron-deficient sites at the 2-, 4-, 5- and 7-positions where both the 1- and 6-nitro group reinforce their electron withdrawal. No such electron-deficient positions are present in 1,7-dinitrophthalene 6 because the electron withdrawing effect of the two nitro groups do not coincide. Thus this electrochemical property of 5 facilitated the reaction with O₂⁻ to form hydroxylated products at the 4- and 5-positions. In contrast, the reaction of 6 was slow, and, in addition to the hydroxylation at the 4-position, a nitro replacement reaction at the 1- and 7-positions by O₂⁻ also occurred.

Since trace amounts of hydroxy or nitro replacement products were obtained when KOH was used instead of KO₂ in these reactions, as shown in Table 2, it is expected that O₂⁻ was the substantial reactant for hydroxylation in this system. Two possible mechanisms for the first step of the hydroxylation by O₂⁻ are considered. One is oxygen dependent: a one-electron reduction by O₂⁻ to form the aromatic radical anion which is followed by the addition of molecular oxygen. The other is oxygen independent: the direct addition of O₂⁻ to the aromatic ring. The reaction was run under Ar to investigate the participation of molecular oxygen. As shown in Table 2, the reaction by 1,3-dinitrophthalane 3 gave a much lower yield than the reaction in the atmosphere, while the reaction yield was increased in the case of 5. Taking into account the one-electron reduction potentials (Epcl) of the mono- and
dinitronaphthalenes and half-wave reduction potentials (E_{1/2})
of O_2, it is concluded that the first step for hydroxylation of 3
and 5 proceeds by a different mechanism, as shown in Chart
1. That is, 3 with an EpC1 (~760 mV) more positive than the
E_{1/2} of O_2 (~877 mV) was easily reduced by O_2, and thus
formed the radical anion combined with O_2 to give the
hydroxylated product. In contrast, the reduction of 5, which has
a more negative EpC1 (~910 mV) than the E1(1/2) of O_2,
was unfavorable under this condition; hydroxylation of 5 pro-
ceeds via the direct addition of O_2. The difference in the
mechanism was also observed by UV–vis spectroscopy. As
shown in Fig. 1a, absorbance at 510 nm, which clearly
indicated the formation of the radical anion of 3, appeared just
after adding the solution of KO_2/18-crown-6 and, along with
the decreasing absorbance at 510 nm, new absorbance as the
result of the addition of O_2 appeared at 380 and 450 nm.
Alternatively, as demonstrated in Fig. 1b, no absorbance associ-
ated with the radical anion of 5 due to the reduction of O_2
was observed, and increasing absorbance at 490 nm originat-
ing from the addition of O_2 was observed under pseudo-
first-order conditions (k_{obs}=2.57×10^{-3} s^{-1}).

The same mechanism as that for the hydroxylation of 3
has been proposed for the formation of 2,4-dinitrophenol by
the reaction of 1-bromo-2,4-dinitrobenzene with O_2 by
Frimer and Rosenthal. On the other hand, the mechanism for
nucleophilic addition by O_2 to 5 is similar to that of hy-
droxylation of 1-nitropyrene by O_2, as previously reported. The
same result was also shown by the reaction of 1-nitro-
naphthalene 1 with KO_2/crown ether (data not shown); the re-
action was oxygen independent and the same spectral change
as that in 5 was observed. The nucleophilic addition of O_2
to 1 was also evidenced by the greater facility of the reaction
in DMF solution as a solvent compared with that in benzene.

Table 2. Effects of Reaction Conditions on Hydroxylation of 3 and 5 with
KO_2/Crown Ether

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction conditions</th>
<th>Products</th>
<th>Yield (%)</th>
<th>Recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>1/8/4, 45</td>
<td>11</td>
<td>81.5</td>
<td>14.8</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>1/8/4, 45[^]</td>
<td>11</td>
<td>38.6</td>
<td>58.0</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>1/8/4, 45[^]</td>
<td>11</td>
<td>0.2</td>
<td>99.4</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>1/8/2, 15</td>
<td>14, 15</td>
<td>40.3, 25.7</td>
<td>25.6</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>1/8/2, 15[^]</td>
<td>14, 15</td>
<td>55.6, 29.9</td>
<td>5.4</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>1/8/2, 30</td>
<td>14</td>
<td>3.6</td>
<td>94.2</td>
</tr>
</tbody>
</table>

[^] The ratio of substrates: KO_2: 18-crown-6 was 1:8:4 for 3 and 1:8:2 for 5. Reaction was run under Ar. KOH was used instead of KO_2.

Chart 1. Possible Mechanism for Hydroxylation of 3 and 5 with KO_2/Crown Ether

Fig. 1. Absorption Spectra of 3 (a) and 5 (b) after Treatment with KO_2/Crown Ether

Spectra were recorded at 2 min intervals over 0—30 min. The spectra represented by the dashed line indicate the absorption of the original 3 and 5 in benzene solution before adding the KO_2/18-crown-6.
solution (data not shown). Therefore it was concluded that
the relative Epcl of nitrated aromatic compounds toward the
El(1/2) of O₂ was an important factor for determining the
mechanism of hydroxylation by \( \text{O}_2^- \).

In conclusion, \( \text{O}_2^- \) is useful for introducing the hydroxy
log group to the nitrated aromatic ring. The electric and steric ef-
fects of the nitro groups are important for determining which
positions are hydroxylated. Two possible mechanisms that de-
pend on the first reduction potential of nitronaphthalenes
are postulated for the first steps in hydroxylation processes
by \( \text{O}_2^- \). Further studies to clarify the subsequent steps are
now in progress.

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