

# On the Mechanism of the Dimethyldioxirane Oxidation of $\sigma^H$ Adducts (Meisenheimer Complexes) Generated from Nitroarenes and Carbanions

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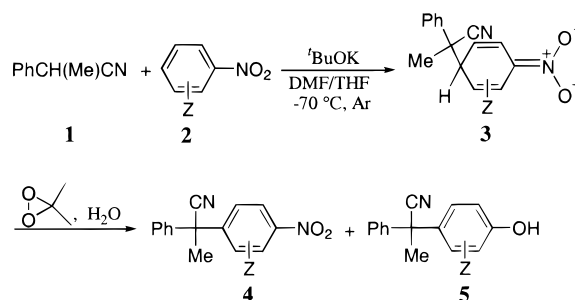
The mechanism of the novel dimethyldioxirane (DMD) oxidation of  $\sigma^H$  adducts (Meisenheimer complexes) generated from nitroarenes and carbanions was elucidated. The proposed mechanism, which is akin to that of the oxidative Nef reaction, is supported by the isolation of the cyclohexadienone intermediate and the lack of a primary kinetic isotopic effect. Protic solvents ( $H_2O$ , MeOH) enhance the reactivity of DMD through intermolecular hydrogen bonding.

## Introduction

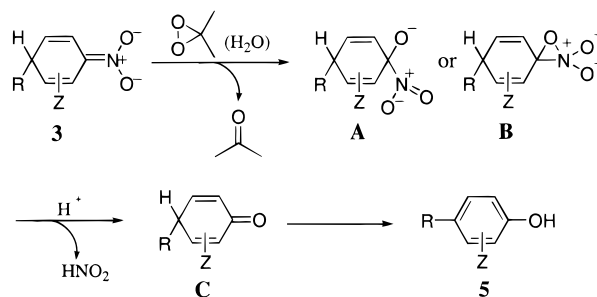
Nucleophiles add reversibly to the unsubstituted *para* and *ortho* positions of nitroarenes to give anionic  $\sigma^H$  adducts (Meisenheimer complexes).<sup>1</sup> These  $\sigma^H$  adducts may be converted into products of nucleophilic replacement of hydrogen in several ways, of which the most important are oxidation and vicarious nucleophilic substitution.<sup>1,2</sup> For example, when the relatively long-lived  $\sigma^H$  adducts **3**, generated in situ from the nitroarenes **2** and the carbanion of 2-phenylpropionitrile (**1**) in liquid ammonia at  $-70\text{ }^\circ\text{C}$ , are treated with potassium permanganate, the substituted nitroarenes **4** are obtained in high yields as the sole products.<sup>3</sup> In contrast, when the in-situ-generated  $\sigma^H$  adducts **3** in DMF–THF are submitted to dimethyldioxirane (DMD) oxidation, the substituted phenols **5** are formed as the major products;<sup>4</sup> the previously<sup>3</sup> observed nitroarenes **4** are formed in small, if any amount (Scheme 1). This unprecedented reaction constitutes the first direct synthesis of substituted phenols from nitroarenes, a novel oxidation of preparative convenience for the synthesis of arenols, which otherwise are cumbersome to obtain.

To date, little if anything is known on the mechanism of the unprecedented DMD oxidation of the  $\sigma^H$  adducts **3** to the corresponding phenols **5**. On one hand, the suggestion<sup>4</sup> that the phenols **5** may arise from the corresponding cyclohexadienone intermediate through oxidative Nef reaction<sup>5</sup> requires verification; on the other hand, the pronounced water effect in enhancing the

## Scheme 1. Dimethyldioxirane (DMD) Oxidation of the $\sigma^H$ Adducts Generated from Nitroarenes and 2-Phenylpropionitrile Carbanion



## Scheme 2. Proposed Mechanism for DMD Oxidation of $\sigma^H$ Adducts



efficiency of this oxidation process demands rationalization.<sup>4</sup> The present paper addresses these aspects and provides experimental evidence for the mechanism of the DMD oxidation of  $\sigma^H$  adducts proposed in Scheme 2.

## Results and Discussion

### Isolation of the Cyclohexadienone Intermediate.

To test the suggestion that the phenolic products **5** arise from tautomerization of the corresponding 2,5-cyclohexadienones,<sup>4</sup> the *para* position in the starting nitroarene should be blocked, to afford a cyclohexadienone which should persist and become isolable. For this purpose, *p*-nitrotoluene (**2b**) was chosen as the substrate, but

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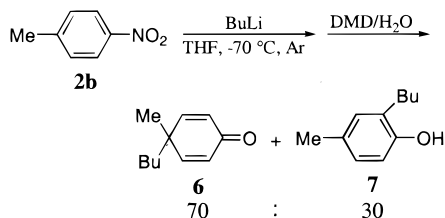
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**Scheme 3. DMD Oxidation of  $\sigma$  Adducts Generated from 4-Nitrotoluene and BuLi**


unfortunately, it does not form sufficiently stable  $\sigma^{\text{H}}$  adducts with the model carbanion of **1**. Oxidation of a mixture of **1** and **2b** in liquid ammonia with  $\text{KMnO}_4$  gave only 2,3-diphenyl-2,3-dicyanobutane, a product of the oxidative dimerization of **1**.<sup>3b</sup> Also the oxidation of such mixture with DMD in THF–DMF did not give the expected product. Presumably the desired  $\sigma^{\text{H}}$  adduct was not formed due to steric reasons.

It is known from Bartoli's work<sup>6</sup> that the Grignard reagents form relatively stable  $\sigma^{\text{H}}$  adducts with nitroarenes, which give alkylated nitroarenes when oxidized with  $\text{KMnO}_4$ . Analogously, in accord with the results of Kienzle,<sup>7</sup> we have found that alkyllithium reagents also can add to nitroarenes; moreover, the latter  $\sigma^{\text{H}}$  adducts may be oxidized by DMD to phenols.<sup>8</sup> When *p*-nitrotoluene (**2b**) was treated with BuLi and then oxidized with DMD, indeed, cyclohexadienone **6** was isolated in a modest yield (16%), along with 7% phenol **7** (Scheme 3). The isolation of the cyclohexadienone **6** confirms that the analogous intermediate **C** (Scheme 2) is the primary product of this oxidation reaction, which subsequently is tautomerized to the corresponding phenol.

Additional experimental evidence for the cyclohexadienone intermediate provides the lack of a kinetic isotope effect (KIE). A  $k_{\text{H}}/k_{\text{D}}$  value of  $1.01 \pm 0.01$  was found in the competitive DMD oxidation of the  $\sigma^{\text{H}}$  adducts, generated from nitrobenzene and 4-deuterio-nitrobenzene with the carbanion of 2-phenylpropionitrile. Since the products of oxidation of  $\sigma^{\text{H}}$  and  $\sigma^{\text{D}}$  adducts are identical, the mixture of recovered nitrobenzene and deuterio-nitrobenzene was analyzed. The lack of a primary kinetic isotope effect indicates that the C–H bond at the *para* position remains intact during the oxidation. In contrast, the  $\text{KMnO}_4$  oxidation of this  $\sigma^{\text{H}}$  adduct in liquid ammonia at  $-70$  °C displays a large KIE value ( $k_{\text{H}}/k_{\text{D}} = 9.9$ ), which indicates that CH-bond breaking is the rate-limiting step.<sup>9</sup> Thus, the slow step of the present DMD oxidation is the formation of the cyclohexadienone intermediate, which subsequently tautomerizes to the phenol. Since the  $\sigma^{\text{H}}$  adducts **3** may be regarded as cyclohexadiene nitronate anions, this transformation is akin to the oxidative Nef reaction,<sup>5</sup> in which the nitronate anion derived from a nitroalkane is converted to a carbonyl group. For example, the formation of 4,4-disubstituted cyclohexadienones was already observed, when the *para*  $\sigma^{\text{H}}$  adducts of  $\text{MeMgBr}$  or  $\text{BuMgBr}$  with *p*-nitrotoluene were acidified with aqueous HCl.<sup>6</sup> Similarly, the addition of an alkylmagnesium halide to 10-alkyl-9-nitroanthracene and subsequent oxidation of the resulting  $\sigma^{\text{H}}$  adducts

**Table 1. Protic Solvent Effects on the DMD and TFD Oxidation of the  $\sigma^{\text{H}}$  Adduct **3a**, Generated from Nitrobenzene (**2a**) and the 2-Phenylpropionitrile Carbanion<sup>a</sup>**

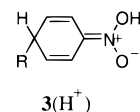
entry	$\text{H}_2\text{O}$ or MeOH (equiv)	yield (%) <sup>b</sup>		mass balance (%)
		nitroarene <b>4a</b>	arenol <b>5a</b>	
1	0	6	47	86
2 <sup>c</sup>	0	traces	traces	54 <sup>d</sup>
3 <sup>e</sup>	1.0	4	77	91
4 <sup>f</sup>	1.0	6	83	100
5 <sup>e</sup>	1.0 <sup>g</sup>	5	33	84
6 <sup>f</sup>	1.0 <sup>g</sup>	4	63	90
7 <sup>h</sup>	0	10	38	53 <sup>i</sup>
8 <sup>h</sup>	1.0	9	32	49 <sup>i</sup>

<sup>a</sup> With 1.0 mmol of **1**, 1.0 mmol of **2a**, 1.1 mmol of  $t\text{BuOK}$ , and 1.2 mmol of DMD in DMF/THF (1:20) under argon gas at  $-70$  °C; DMD solution was predried two times over fresh molecular sieves for 2 days each. <sup>b</sup> Yields of isolated materials after chromatography. <sup>c</sup> DMD was dried over  $\text{P}_2\text{O}_5$  and then over  $\text{K}_2\text{CO}_3$ . <sup>d</sup> Poor mass balance due to low recovery of **1**. <sup>e</sup>  $\text{H}_2\text{O}$  (MeOH) was added first to the reaction mixture and 5 min later the DMD solution. <sup>f</sup> DMD was added first to the reaction mixture and 5 min later the  $\text{H}_2\text{O}$  (MeOH). <sup>g</sup> MeOH was added instead of water. <sup>h</sup> 1.2 mmol of (trifluoromethyl)methyldioxirane (TFD) was added instead of DMD. <sup>i</sup> Poor mass balance due to formation of some unidentified products.

by  $\text{Pb}(\text{OAc})_4$  gave 10,10-dialkylanthrones.<sup>10</sup> Consequently, DMD has been demonstrated herein as a good oxidant for the oxidative Nef reaction,<sup>11</sup> which establishes the link between these two seemingly distinct reactions.

**The Water Effect on the Oxidation Process.** The results of the pronounced water effect in enhancing the yield of the phenol product in the DMD oxidation of  $\sigma^{\text{H}}$  adducts **3a** are collected in Table 1. Oxidation of **3a** with a solution of DMD in acetone, prepared according to the standard procedure,<sup>12</sup> gave the phenol in a moderate yield of 47% (entry 1). When 1 equiv of water was added to the reaction mixture, either before or after the addition of DMD, the yield of phenol **5a** was almost doubled (entries 3 and 4). When a rigorously dry DMD solution was employed, the yield of the phenol diminished dramatically (entry 2). A similar water effect has also been observed in the DMD oxidation of nitronate anions (prepared by deprotonation of nitroalkanes) to carbonyl products (the oxidative Nef reaction).<sup>11</sup>

One possible reason for the observed water effect is that the  $\sigma^{\text{H}}$  adducts **3** might react with water to form the protonated intermediate **3(H<sup>+</sup>)**, which could be more



prone to oxidation than the anion **3**. To clarify this possibility, the DMD oxidation of benzophenone oxime (**8**) was conducted under neutral and basic conditions as a model reaction (Scheme 4).

While the oxime **8** itself resisted oxidation by DMD to benzophenone, in the presence of *t*-BuOK, a quantitative conversion was achieved. Consequently, it appears that the oxime anion **8<sup>-</sup>** is oxidized first to the nitronate anion

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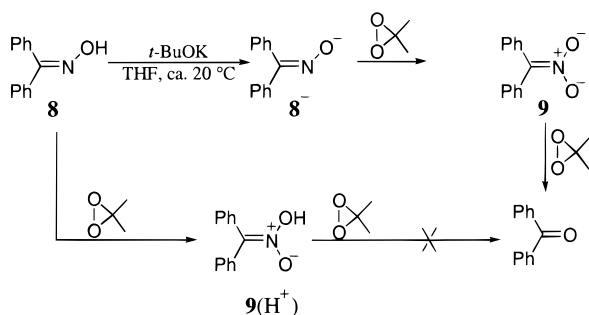
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**Scheme 4. DMD Oxidation of the Benzophenone Oxime Anion**

**9** and subsequently to benzophenone; in contrast, the protonated nitronate **9(H<sup>+</sup>)** survives further oxidation by DMD. In view of the similarity between the oxidized oxime species **9** and **9(H<sup>+</sup>)** and the  $\sigma^H$  adducts **3** and **3(H<sup>+</sup>)**, these results suggest that the nitronate anion **3** (the  $\sigma^H$  adduct) and not the protonated intermediate **3(H<sup>+</sup>)** is the likely species to be oxidized in the DMD reaction of  $\sigma^H$  adducts. Additionally, the oxidation of the protonated  $\sigma^H$  adduct **3(H<sup>+</sup>)** is also ruled out because the use of aqueous  $\text{NH}_4\text{Cl}$  instead of water inhibits the DMD oxidation. The possibility that water intervenes after the oxidation step is discounted by the lack of a primary kinetic isotope effect, which establishes that the removal of the *para* hydrogen atom is not the rate-limiting step, but presumably the oxidation of the  $\sigma^H$  adduct **3** to the cyclohexadienone intermediate.

It is well-known in the literature that the protic solvents water and MeOH accelerate DMD oxidations through hydrogen bonding with the dioxiranes.<sup>13</sup> Since the  $\sigma^H$  adduct **3** is stabilized through conjugation, it is quite resistant against oxidation by DMD. Water, however, enhances the reactivity of DMD through hydrogen bonding and thus facilitates the oxidation process, and the phenol yield is increased by circumvention of side reactions of the  $\sigma^H$  adduct. Also MeOH serves as promoter of this oxygen transfer, since the addition of 1.0 equiv of MeOH (Table 1, entry 6) after DMD afforded a good yield (63% versus 83% in  $\text{H}_2\text{O}$ ) of the phenol **5a** (Table 1, entry 6); however, unlike in the case of water, the reverse addition showed no effect for MeOH (Table 1, entry 5).

The use of the much more reactive (ca. 600 to 1000-fold)<sup>14</sup> methyl(trifluoromethyl)dioxirane (TFD) as oxidant

proved to be disadvantageous. Although the conversions of the substrates were very high (>90%), the yields of phenol **5a** were low (32–38%), irrespective of whether water was added or not (Table 1, entries 7 and 8). Therefore, the DMD oxidation of the  $\sigma^H$  adducts **3** is a chemoselective reaction, presumably because DMD preferentially reacts with the more electron-rich C=N double bond to give the cyclohexadienone. In contrast, the much more reactive TFD apparently also oxidizes the cyclohexadienone double bonds in the  $\sigma^H$  adduct **3**, which leads to a complex mixture of undefined products. The inherent high reactivity of TFD is presumably also responsible why no assistance by water is necessary.

**Mechanism of DMD Oxidation of  $\sigma^H$  Adducts.** On the basis of the above facts, we propose that the mechanism in Scheme 2 operates in the DMD oxidation of  $\sigma^H$  adducts. On account of the enhanced reactivity through hydrogen bonding with water, DMD oxidizes the  $\sigma^H$  adducts **3** to the transient species **A** or **B** in the rate-limiting step. Elimination of a nitrite ion (the nitrite ion is expected to be oxidized to the nitrate ion under the reaction conditions and does not accumulate for detection) from the **A** or **B** intermediates affords cyclohexadienone **C**, which tautomerizes to the more stable phenols **5**. This mechanism is analogous to that of the oxidative Nef reaction with  $\text{KMnO}_4$ <sup>15</sup> or DMD<sup>11</sup> as oxidants; however, while  $\text{KMnO}_4$  has been successfully employed in the Nef reaction to convert nitronate anions to carbonyl products,<sup>15</sup> in the present case it converts  $\sigma^H$  adducts **3** to the nitroarenes **4** instead of the arenols **5**.<sup>3</sup> Thus, the DMD oxidation of the  $\sigma^H$  adducts of nitroarenes **2** to the corresponding phenols is a unique process of preparative value in aromatic substitution chemistry.

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**Supporting Information Available:** Experimental section and GC-MS spectra. This material is available in the Internet under <http://pubs.acs.org>.

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