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Reactivity of Phthalimide-*N*-oxyl: A Kinetic Study

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The reactivity of phthalimide-*N*-oxyl radical (**2**), which is produced by an electrochemical one-electron oxidation of *N*-hydroxyphthalimide (**1**), was investigated. The self-decomposition of **2** obeyed second-order kinetics with respect to itself and the rate was little affected by changing the temperature or the concentration of dissolved oxygen, water or added base. In the reaction between **2** and benzhydrol or its α -deuterated derivative, the decay of the radical was first-order with respect to each component. The observed large deuterium isotope effect ($k_H/k_D = 10.6$ at 25°C) is attributed to the rate-limiting hydrogen abstraction. Rate measurements were performed on the reaction with 24 other substrates which have one or more hydrogen atoms on a benzylic or allylic position or on a carbon adjacent to a hetero atom.

Keywords—*N*-hydroxyphthalimide; phthalimide-*N*-oxyl; hydrogen abstraction; indirect electrochemical oxidation; EC catalytic process

In our laboratory it has been shown that *N*-hydroxyphthalimide (**1**) can act as an effective electrochemical mediator in a variety of oxidation reactions. Many sorts of compounds including alcohols,¹⁾ those having a benzylic carbon or α -carbon to a hetero atom,²⁾ olefins,³⁾ amides and lactams,⁴⁾ ketals,⁵⁾ and aldehyde acetals⁶⁾ were found to be substrates for the mediation. The reaction mechanism has been considered to be as shown in Chart 1, in which the phthalimide-*N*-oxyl radical (**2**) acts as the oxidant. However, chemical characterization of the radical has not yet been carried out, though it would be useful for a precise understanding of the process. This paper reports the results of quantitative evaluation

Chart 1

Fig. 1. Cyclic Voltammograms of **1**

In acetonitrile containing 0.1 M NaClO₄ and 10 mM pyridine: (a) without, (b) with 50 mM isochroman. Glassy carbon electrode (area = 0.071 cm²); voltage sweep rate, 50 mV s⁻¹; concentration of **1**, ca. 5 mM.

of the reactivity of **2** in self-decomposition and in the reaction with substrates.

Results and Discussion

Nature of **2** in the Absence of the Substrates

On cyclic voltammetry in acetonitrile containing 0.1 M sodium perchlorate and an excess of pyridine,⁷⁾ **1** showed a nearly reversible redox couple at 0.78 V vs. S.C.E. (Fig. 1a). The normalized peak current, 15.6 $\mu\text{A}/\text{mm}$, for the oxidation wave was comparable with those of 4-substituted 2-cyano-2-phenylvinylamines, the electrode process of which was shown to be a one-electron transfer.⁸⁾ The formation and the decay of **2** were found to be synchronized with spectral changes at around 400 nm. As shown in Fig. 2, the absorbance at that wavelength was monitored during a macro scale electrolysis and the following open circuit relaxation.⁹⁾ Since constant current electrolysis was used, a linear dependence between the increasing optical density and time (*i.e.*, consumed electricity) was observed at the earlier part of the run. From the slope, the apparent absorptivity of **2** could be estimated.¹⁰⁾ An electron spin resonance (ESR) spectrum was also obtained from the solution, and the data ($A_N=4.77\text{ G}$ (1N), $A_H=0.4\text{ G}$ (2H), $g=2.0070$) were close to the reported values.¹¹⁾

Fig. 2. Absorption-Time Curve for the Generation and Decay of **2** and the Second-Order Plot for the Self-Decomposition

Conditions were as follows: concentration of **1**, 5 mM; pyridine, 5 mM; constant current electrolysis (5 mA); monitored wavelength, 400 nm; temperature, 25 °C. The ordinate of the second-order plot corresponds to $(A_0 - A)/A_0A$, where A_0 and A are the absorbance at $t=0$ and t , respectively.

Chart 2

From the right half of the absorbance–time curve in Fig. 2, a good second-order relationship to the radical itself was shown with a rate constant of $24.1 \text{ l mol}^{-1} \text{ s}^{-1}$. Similar measurements were carried out by changing the following variables; initial concentration of **2**, presence and absence of dissolved oxygen, temperature ($15\text{--}35^\circ\text{C}$) and the base concentration. All the observed rate constants were scattered in the range of $\pm 10\%$, so that a simple bimolecular reaction with a very small activation energy was suggested.

To investigate the products of the self-decomposition of **2**, exhaustive electrolysis of the solution of **1** was carried out at 0.90 V. The consumed electricity was 2.4 F/mol and the trimer (**3**) was isolated from the resulting solution in 71% yield. Phthalic acid (2.5%), phthalic anhydride (8%), phthalimide (trace) and recovered **1** (3.5%) were also detected by high-performance liquid chromatography (HPLC). As judged from the kinetic data, disproportionation of the radical **2**, probably including the formation of a molecule of **1** and an *N*-oxonium cation or its equivalent, can be presumed. While little information about the subsequent processes is available, the pathway in Chart 2 can be deduced from the results on oxidation of hydroxamic acids to form *N,O*-diacylhydroxylamines.¹²⁾ Since the acyl cation **4** can be considered as an acylating agent, **5** will be produced by reaction with **1**. One more nucleophilic attack of **1** on the other carbonyl carbon in **5** is necessary to form **3**, but the details of the process are not clear at present. If a water molecule contaminating the medium reacts with **4** as a nucleophile, a carboxylic acid **6** will be produced instead of **5**. The minor products, phthalic acid and phthalic anhydride may be formed through **6** by reaction with another molecule of water or by intramolecular cyclization, respectively.

Nature of **2** in the Presence of the Substrates

Figure 1b shows a voltammogram of **1** in the presence of isochroman, which was chosen because of its highest reactivity toward **2** among the substrates tested in the present study (see Table II). A remarkable increase in the anodic peak current with complete disappearance of the cathodic counterpart was demonstrated. The additive alone did not show any redox wave in the potential region, so this behavior is attributable to an EC catalytic process¹³⁾ in which the turnover of **2** to **1** by isochroman takes place at an appreciable rate even in the diffusion layer.

To investigate the reaction process in the bulk solution, benzhydrol was chosen, mainly because of its moderate reactivity toward **2** and the ease of obtaining the α -deuterated derivative. The procedures were similar to those of the self-decomposition, but a stopped-flow technique was used. With a large excess of the alcohol a good first-order decay of **2** was demonstrated. The observed rate constants, k_{obs} , for the substrate and its α -deuterated derivative under various conditions are listed in Table I. The values in the last column correspond to the second-order rate constants obtained by dividing the k_{obs} by the substrate concentration. The constancy of the values in runs 1–3 indicates that the reaction is also first-order with respect to the substrate. These rates were little affected by changing the pyridine concentration (run 4). A remarkably large deuterium isotope effect, $k_{\text{H}}/k_{\text{D}} = 10.6$, which falls into a theoretical maximum region,¹⁴⁾ was observed (runs 2 and 8), indicating that the reaction rate is controlled by the α -C-H (or D) bond cleavage. The activation energies were estimated to be 4.8 and 6.7 kcal mol⁻¹ for α -H and α -D substrates, respectively. The difference between the two values is comparable with that obtained theoretically ($1.21 \pm 0.04 \text{ kcal mol}^{-1}$).¹⁵⁾ On the other hand, the activation energies seem appreciably smaller than those reported in the analogous hydrogen abstraction from cumene by benzoyl *tert*-butyl nitroxide (17.9 kcal mol⁻¹),¹⁶⁾ and by di-*tert*-butyliminoxyl (16.8 kcal mol⁻¹).¹⁷⁾ However, it is generally known that the magnitude of the value in this type of reaction depends not only on the dissociation energies of the bonds to be cleaved and formed, but also on the structures of the substrates and the radicals.^{15,18)} The smaller value in the present case may be attributed to

the structural characteristics of the radical **2**, in which the nitrogen atom is fixed on the ring and flanked by the two carbonyl groups.

It has been reported that benzhydrol is oxidized in the mediating system, yielding benzophenone with good efficiency.¹⁾ Since the consumed electricity based on the substrate was 2 F/mol, participation of another molecule of **2** has been claimed for this indirect oxidation. However, no information concerning the latter process could be obtained from the present results.

Table II summarizes the second-order rate constants obtained for a variety of substrates. Most of these compounds were chosen because their oxidation products in the mediating system have been at least partly elucidated. From the data, we may make the following generalizations, though only qualitatively. First, all the substrates tested here have one or more hydrogen atoms on a benzylic or allylic position or on carbon adjacent to a hetero atom. Such activation seems to be essential for exhibiting reactivity toward **2**, and duplication is more effective. Some examples of the latter case are found in the following pairs: ethylbenzene < benzylmethylether ($\approx$ benzyl alcohol), tetralin < isochroman, isopropanol < benzhydrol.

Second, cyclic substrates show faster rates than the corresponding acyclic ones. Cyclohexanol, tetralin and isochroman are more reactive than isopropanol, ethylbenzene and benzylmethylether, respectively.

TABLE I. Rate Data for the Reactions of the Radical **2**^{a)} with Benzhydrol and Its α -Deuterated Derivative

Run	Substrate	Concentration (mm)	Temperature (°C)	k_{obs} (s ⁻¹) ^{b)}	k (l mol ⁻¹ s ⁻¹)
1	Ph-CH(OH)-Ph	10	25	0.384	38.4
2		50	25	1.95	38.9
3		100	25	3.32	33.2
4 ^{c)}		50	25	1.66	33.2
5		50	15	1.23	24.6
6		50	35	2.13	42.6
7	Ph-CD(OH)-Ph	50	15	0.127	2.54
8		50	25	0.182	3.64
9		50	35	0.270	5.40

a) Initial concentrations, ca. 0.5 mm. b) Average value of at least three different runs. c) Pyridine concentration, 50 mm (others were 5 mm).

TABLE II. Second-Order Rate Constants^{a)} of the Reaction of the Radical **2** with Various Substrates

Substrate	k (l mol ⁻¹ s ⁻¹)	Substrate	k (l mol ⁻¹ s ⁻¹)
Isopropanol	1.89	Cyclohexene ^{c, d)}	20.2
Cyclohexanol ^{b)}	4.52	<i>trans</i> -4-Octene ^{d)}	12.8
β -Phenethyl alcohol	0.776	2,3-Dimethyl-2-butene ^{d)}	77.6
Benzyl alcohol	15.6	Tetrahydrofuran ^{c)}	2.88
Anise alcohol	51.8	Tetrahydropyran	Very slow ^{f)}
<i>p</i> -Nitrobenzyl alcohol	10.3	Dibutyl ether	1.50
Ethylbenzene ^{c)}	1.85	Dibutyl sulfide	36.3
Benzylmethylether ^{c)}	10.9	Tetrahydrothiophene ^{c)}	96.2
Isochroman ^{c)}	156	Tetrahydrothiopyran	15.3
Fluorene ^{c)}	26.2	<i>N</i> -Acetylpyrrolidine ^{e)}	47.6
Tetralin ^{c)}	43.2	<i>N</i> -Benzoylpyrrolidine ^{e)}	26.2
Cyclopentene ^{d)}	28.4	<i>N</i> -Benzoylpiperidine ^{e)}	0.576

a) Determined from at least three different kinetic runs. b—e) The products of the indirect oxidation were reported in refs. 1, 2, 3 and 4, respectively. f) Less than 0.2 l mol⁻¹ s⁻¹.

Third, higher reactivity of five-membered-ring substrates compared to the corresponding six-membered ones, except for the case of cycloalkene, is also suggested. These results account for the poor efficiencies of the six-membered substrates in the mediating system. Tetrahydrothiopyran and *N*-benzoylpiperidine gave the oxidation products in only 8 and 9% yields, respectively,¹⁹⁾ while the corresponding five-membered analogs gave the products in 30 and 79% yields, respectively.^{2,4)} Furthermore, tetrahydropyran was practically not oxidizable in the system but tetrahydrofuran gave the lactone in 11% yields.²⁾

Although quantitative treatment of the structure–reactivity relationship of the substrate toward **2** was not successful, the chemical characterization of the reaction has been achieved. Advantages of **2** as a reagent for the hydrogen abstraction reaction have also been revealed. It shows reactivity with a wide range of compounds, its generation can be easily controlled electrochemically in terms of the rate and the amount, and the direct determination of the radical concentration is possible by spectrophotometric measurements.

Experimental

Materials—*N*-Hydroxyphthalimide was obtained from Tokyo Kasei Kogyo Co. (>99%). α -Deuterated benzhydrol was prepared from benzophenone by LiAlD_4 (Merck; >98%) reduction in tetrahydrofuran followed by recrystallization from methanol–water, MS m/z : 185 (M^+). Acetonitrile was purified as described previously.²⁰⁾ All other chemicals were from commercial sources and were used with or without appropriate purification.

Apparatus—Cyclic voltammetry and controlled potential electrolysis were carried out essentially as described previously.⁸⁾ Kinetic experiments were carried out using JASCO UVDEC-1 double beam and Union Giken RA-601 stopped-flow spectrophotometers and a Hokuto Denko HA-104 potentiostat-galvanostat. A Union Giken RA-405 kinetic data processor was used for monitoring the fast reactions.

Kinetic Measurements of the Self-Decomposition of 2—A Pyrex cylindrical vessel (diameter; 2.6 cm, volume; 20 ml) fixed on a magnetic stirrer was placed in the double beam spectrophotometer so that the light would cross the center. The light-path length (2.60 cm) was determined optically. A glassy carbon plate (anode) and a platinum wire (cathode) were placed in the cell. The constant current electrolysis of the solution of **1** was carried out for an appropriate duration followed by circuit opening. The absorption at the selected wavelength was recorded throughout the run.

Product Analysis of the Self-Decomposition of 2—A typical example is described.

A solution of **1** (326 mg) dissolved in 50 ml of acetonitrile containing 0.1 M NaClO_4 and pyridine (790 mg; 5 eq) was subjected to electrolysis at 0.90 V at a glassy carbon plate anode in an H-type cell. Up to the time when the current became <2% of the initial value, 455 C (2.4 e per molecule) had been consumed. The electrolytic solution was evaporated and the residue was washed with ether and water. The resulting solid was recrystallized from acetonitrile and identified as *O,O'*-(1,2-phenylenedicarbonyl)-bis-*N*-hydroxyphthalimide (**3**), (216 mg, 71%), mp 229–233 °C. Anal. Calcd for $\text{C}_{24}\text{H}_{12}\text{N}_2\text{O}_8$: C, 63.16; H, 2.65; N, 6.14%. Found: C, 63.25; H, 2.54; N, 6.20. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1780, 1740, 1180, 1130, 990, 875, 790, 700. NMR (CDCl_3) δ : 7.5–8.3. MS m/z : 457 ($\text{M}^+ + 1$). The above ether washings were collected and evaporated. The resulting residue was dissolved in methanol and adjusted to 20.0 ml in a volumetric flask, then subjected to HPLC measurements. A Waters 6000-A solvent delivery system, a Shimadzu SPD-2A spectrophotometric detector and a Bondapack C_{18} -Corasil column were used, with 50% aqueous methanol as the solvent. Identification of minor products was performed by comparing the retention time in HPLC and the *Rf* values in silica gel thin layer chromatography with those of authentic samples. To confirm the structure of **3**, the following derivatization was also carried out. The trimer (1.51 g) was suspended in 30 ml of 40% aqueous ethanol containing 10% NaOH and refluxed for 24 h. The solution was acidified with HCl and extracted with ethyl acetate (20 ml $\times$ 7). The extract was dried over Na_2SO_4 and evaporated. Practically pure phthalic acid (83% from **3**) was obtained by washing the residue with chloroform.

Kinetic Measurements of the Reaction with the Substrates—In one of the two reservoirs of the sample mixing unit of the stopped-flow spectrophotometer, platinum wire working and counter electrodes were attached so that the accumulation of **2** under appropriate electrolytic conditions could be achieved. Then, a part of the solution was mixed rapidly with a solution which was stored in the other reservoir containing the substrate to be examined. The standard reaction conditions were as follows (concentrations are those after mixing): **1**, 5 mM; pyridine, 5 mM; substrate, 50 mM; radical concentration generated from **1**, ca. 0.5 mM; temperature, 25 °C. The decay of the absorption at 400 nm was followed.

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