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## ANTIOXIDANT ACTIVITY OF INTRAMOLECULARLY HYDROGEN BONDED 2-AMINOPHENOLS

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### Abstract

The antioxidant activities of five classes of 2-aminophenol (model compound) and 2-aminophenols with substituent at the phenyl ring were studied in the oxidation of tetralin induced by an azo-initiator at 61 °C. 2-Aminophenols with electron-donating groups at the 4-position exhibited higher antioxidant activity than that of the model compound. However, introduction of the methoxy group at the 4-position reduced the antioxidant activity by 8 % that of the model compound. 2-Aminophenols with electron-donating groups at the 5-position have little effect on the antioxidant activity. 2-Aminophenols with electron-donating groups at both the 4- and 6-positions showed remarkable antioxidant activity. These results were discussed in terms of the hydrogen bonding effect and bond dissociation energies of the O-H and NH-H bonds.

### 1. Introduction

The inhibition of radical polymerization is very important in the chemical industry as a way of preventing premature polymerization during the processing, storage and transportation of unsaturated monomers. At the same time, oxidation is the main cause of deterioration among rubber products, plastics and lubricating oils. Consequently, the inhibition of these oxidations has attracted much attention and various natural and synthetic antioxidants are now on the market.

In some earlier studies of the antioxidant activity of diphenylamine derivatives, it has been demonstrated that diphenylamines with an amino group, as a substituent at the *ortho* position to the hydroxy group were potently antioxidants.<sup>1,2)</sup> Therefore, in this work, we have prepared several 2-aminophenols which have substituents, such as methyl, ethyl, methoxy, phenyl and *tert*-butyl groups at the phenyl ring, and measured the antioxidant activity for the oxidation of tetralin initiated by an azo-compound. In addition, we tried to explain the antioxidant activity of these compounds through O-H and NH-H bond dissociation energies.

### 2. Experimental

#### 2.1. Assay for antioxidative activity

The rate of oxygen absorption was measured as a function of time under 760 Torr

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(1 Torr = 133.322 Pa) of O<sub>2</sub> with 50.0g of tetralin containing an antioxidant [1.03 mM] and  $\alpha$ ,  $\alpha'$ -azobisisobutyronitrile (AIBN) [10.0 mM] as the initiator. The oxidation temperature was maintained at 61  $\pm$  0.1 °C. The induction period ( $t_{inh}$ ) value was graphically determined from the length of time between initiator injection and the point of intersection of the tangents to the oxidation curve corresponding to the initial inhibited and uninhibited rates of oxidation.

## 2.2. Molecular orbital calculations

The bond dissociation energies of the NH-H ( $D(\text{NH-H})$ ) and O-H ( $D(\text{O-H})$ ) bonds were obtained from the enthalpy of the optimum structures of antioxidants and relative radicals using the technique of AM1 in WinMOPAC ver.2.0 (Windows), as follows:

$$D(\text{NH-H}), D(\text{O-H}) \text{ (kJ/mol)} = E_r + E_H - E_O$$

where  $E_r$ : enthalpy of radical,  $E_H$ : enthalpy of hydrogen radical,  $E_O$ : enthalpy of antioxidant.

## 3. Results and Discussion

### 3.1. Inhibition of oxidation of tetralin by 2-aminophenols assessed by induction period, $t_{inh}$

The antioxidants examined in this study were divided into the four classes shown in Fig. 1: 2-aminophenol (**1**) (referred to as the model compound), 4-substituted 2-aminophenols (**2**), 5-substituted 2-aminophenols (**3**), 6-substituted 2-aminophenols (**4**), and 4, 6-disubstituted 2-aminophenols (**5**). Fig. 2 shows the results of the oxidation of tetralin initiated by AIBN in the absence (control) and presence of **1** and **2** as antioxidants. The oxidation proceeded smoothly in the absence of an antioxidant without a noticeable  $t_{inh}$ , and a constant rate of oxygen uptake was observed. In the presence of **1** and **2**, the rate of oxygen uptake was significantly suppressed and a distinct induction period was observed. As shown in Fig. 2, the rate of oxidation after the induction period was similar to that seen in the absence of antioxidant.

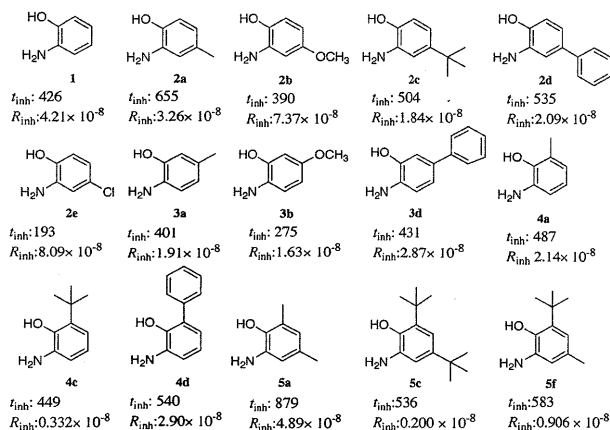


Fig. 1 Summary of  $t_{inh}$  (min) and  $R_{inh}$  (M/sec) for antioxidants used in this study.

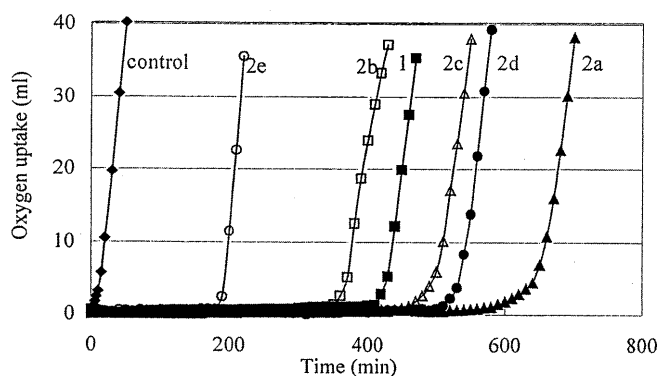


Fig. 2 Rate of oxygen uptake in the oxidation of tetralin initiated by AIBN in the absence (control) and presence of 2-aminophenols at 61 °C under oxygen

The  $t_{inh}$  value shows how well the antioxidant traps the peroxy radicals. The data regarding the relative antioxidant activity of **1-4**, denoted by  $t_{inh}$ , is shown in Table 1 and Fig. 1. By comparing the substituents on the phenyl ring in **1** and **2**, electron-donating groups at the 4-position, except for the methoxy group, have the effect of increasing the  $t_{inh}$ , methyl group by 1.54 times, the *tert*-butyl group by 1.18 times, and the phenyl group by 1.26 times, as compared to those of model compound **1**. However, an electron-withdrawing group, such as the chlorine atom is 0.45 times less active as antioxidant than compound **1**. The compounds for class **3** with electron-donating groups at the 5-position, except for **3b** with the methoxy group, gave about the same  $t_{inh}$  values as those for the model compound **1**, indicating that the electron-donating groups have no effect on antioxidant activity, at least in our oxidation conditions. The compounds of class **4** show 5-27 % higher antioxidant activity as measured by the  $t_{inh}$  than model compound **1**.

Table 1 Relative antioxidant efficiency denoted by  $t_{inh}$  values of 2-aminophenols

R	H	Me	OMe	<i>t</i> -Bu	Ph	Cl	<i>t</i> -Bu Me
	1 (1)	1.54 (2a)	0.92 (2b)	1.18 (2c)	1.26 (2d)	0.45 (2e) <sup>a)</sup>	-
	1	0.94 (3a)	0.65 (3b)	-	1.01 (3d)	-	-
	1	1.14 (4a)	-	1.05 (4c)	1.27 (4d)	-	-
	1	1.94 (5a)	-	1.26 (5c)	-	-	1.36 (5f)

a) Compound number

The results for **1-4**, as measured by the  $t_{\text{inh}}$ , suggest that the antioxidant activity of substituted 2-aminophenols depends on the position and nature of substituents. That is, 2-aminophenols with electron-donating group at the 4- and 6-positions exhibit higher antioxidant activity than model compound **1**. However, electron-donating groups at the 5-position have no effect on antioxidant activity. These results clearly suggest that the active site for the antioxidant potential of **1-4** is the phenolic OH group, rather than the NH<sub>2</sub> group.

Contrary to our results, Mukai et al have reported the rate constants of tocopherols and tocopherol model compounds with stable phenoxyl radical.<sup>3</sup> By comparing the rate constants for 10 kinds of tocopherol derivatives, they suggested that the antioxidant activity of tocopherol models depends on the number of alkyl substituents on the aromatic ring, rather than on the position of substitution.

It was of special interest to design an antioxidant which possesses both alkyl groups at the 4, 6-positions, as achieved in compound **5**. Incorporation of two electron-donating methyl groups causes a remarkable increase in antioxidant activity. The compound **5a** exhibits  $t_{\text{inh}}$  values 1.94 times that of compound **1**. However, the more bulky *tert*-butyl group at the 6-position showed no remarkable increase in antioxidant activity. The compounds **5c** and **5f** have little effect on the antioxidant activity; there is only a 26% and 36% increase in the  $t_{\text{inh}}$ , respectively, as compared to **1**. In the case of **4c**, 2-amino-6-*tert*-butylphenol has little effect on the antioxidant activity, as compared to **4a**. These results are in general agreement: *ortho* substituents on alkyl phenols, such as methyl and ethyl groups, exert two opposite effects on the antioxidant activity. The first is an accelerating effect, due to electron release from the substituent, and the second, a retarding effect, due to steric factors. However, more bulky *ortho* alkyl substituents, such as the *tert*-butyl group, cause a significant lowering in antioxidant activity.<sup>4,6)</sup>

### 3.2. ArO-H and ArNH-H bond dissociation energies

Efficient phenols and aromatic amines are known to terminate the peroxidation of free radical chains by donating a hydrogen atom from the O-H and NH-H bonds. Therefore, efficient antioxidants are expected to possess both low O-H ( $D(\text{O-H})$ ) and NH-H ( $D(\text{NH-H})$ ) bond dissociation energy (BDE). The substituent effect on the O-H BDE has been studied by many research teams. For example, *para*-substituted phenols with electron-donating groups, such as NR<sub>2</sub> and OR, significantly reduce the O-H BDE, while electron-withdrawing groups such as NO<sub>2</sub>, CN and COR have the opposite effect.<sup>7,8)</sup> Therefore, we calculated the  $D(\text{N-H})$  and  $D(\text{O-H})$  for the selected aminophenols with a semiempirical AM1 molecular orbital calculation using the program WinMOPAC ver. 2.0.<sup>9)</sup> The BDE's of NH-H and O-H are listed in Fig. 3. By comparing the  $D(\text{O-H})$  and  $D(\text{NH-H})$  for *ortho*-, *meta*- and *para*-aminophenols and methyl substituted 2-aminophenols, values of  $D(\text{O-H})$  were calculated and found to be weaker than  $D(\text{NH-H})$  by 25.1~64.8 kJmol<sup>-1</sup>. These BDE values are in agreement with the observed antioxidant activity denoted by  $t_{\text{inh}}$  values.

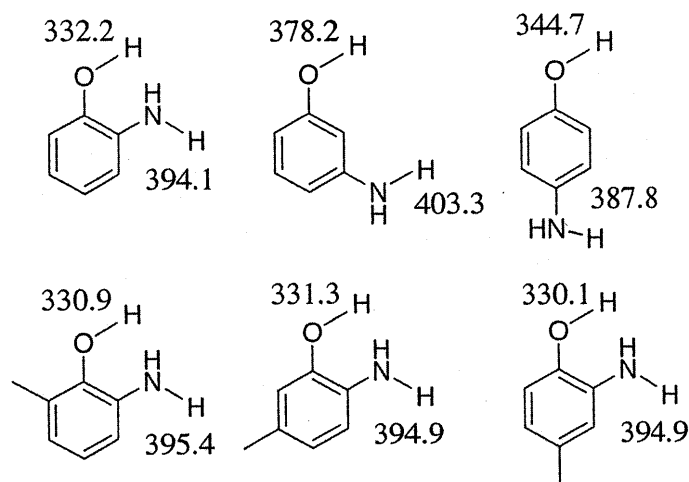


Fig. 3 Calculated bond dissociation energy (kJ/mol),  $D(\text{O-H})$  and  $D(\text{NH-H})$ , for selected aminophenols

As described in a previous section, the active site for the antioxidant ability of **1-5** is the phenolic OH group, rather than the  $\text{NH}_2$  group. Furthermore, the  $D(\text{O-H})$  values obtained for aminophenols increased in the order: 2-aminophenol **1** ( $332.2 \text{ kJmol}^{-1}$ ) > 4-aminophenol ( $344.7 \text{ kJmol}^{-1}$ ) > 3-aminophenol ( $378.2 \text{ kJmol}^{-1}$ ). For 2-aminophenol **1**, hydrogen bonding can occur between the amino hydrogens and the phenolic oxygen atom. This will labilize the O-H bond and hence cause a decrease in the O-H BDE. Moreover, the corresponding phenoxyl radical may be stabilized relative to the 2-aminophenol (see Fig. 4). In agreement with this, the order of activity of aminophenols with respect to the position of the  $\text{NH}_2$  group in terms of the  $t_{\text{inh}}$  value are 2-aminophenol **1** ( $t_{\text{inh}} = 426 \text{ min}$ ) > 4-aminophenol ( $t_{\text{inh}} = 352 \text{ min}$ ) > 3-aminophenol (inactive). Ingold et al have reported the  $D(\text{O-H})$  of phenol derivatives with methyl, methoxy and amino groups.<sup>10</sup> They reported that amino groups in the *ortho* position have a remarkably large O-H bond-weakening effect. The compounds and substituted amines derived from these compound may represent a new line of investigation in the search for more effective antioxidants.

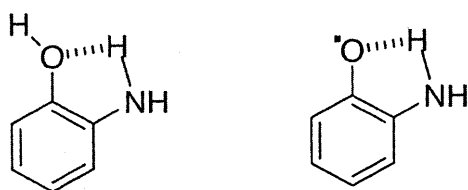


Fig. 4 Intramolecularly hydrogen bonded *ortho*-aminophenol and its phenoxyl radical

### 3.3. Antioxidant activity of 2-aminophenols denoted by $R_{inh}$

In general, characterizations of the antioxidant activities can be expressed by two values,  $k_{inh}$  and  $t_{inh}$  and/or  $n$ , where  $k_{inh}$  is the rate constant of inhibition and  $n$  is the stoichiometric factor. Instead of the  $k_{inh}$ , we used the rate of oxidation ( $R_{inh}$ ) for evaluation of antioxidant activity.<sup>11)</sup> The  $R_{inh}$  shows how well the antioxidant reduces the rate of oxidation. Experimental results for determination of antioxidant activities, as measured by the  $R_{inh}$ , are given in Fig. 1. The results listed in Fig. 1 indicate that the 2-aminophenols **2**, except for **2b** and **2e**, have reactivities similar to or slightly higher than the model compound **1**. In general, the introduction of electron-donating groups to *ortho* and *para* positions in the phenol ring increases the antioxidant activity, whereas electron-withdrawing groups decrease it.<sup>3,12)</sup> However, the antioxidant activity of 2-amino-4-methoxyphenol **2b** is only half as active as **1**. We suggest that intermolecular hydrogen bonding can occur between the hydrogen of the O-H group and the methoxy oxygen atom, and as a result the O-H bond is stabilized. Hence there is a decrease in antioxidant activity (see Fig. 5). In comparing the other 2-aminophenols **3-5**, we can see that 2-aminophenols with *tert*-butyl group possess a truly remarkable antioxidant potential. 2-Amino-4,6-di-*tert*-butylphenol **5c**, especially, has a significantly higher antioxidant potential, as denoted by  $R_{inh}$ , than the other 2-aminophenols studied.

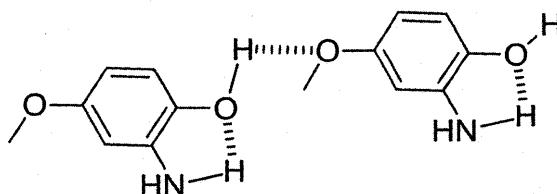


Fig. 5 Intermolecularly hydrogen bonded 2-amino-4-methoxyphenol **2b**

In conclusion, the overall efficiency of an antioxidant is determined by the induction period,  $t_{inh}$ , as well as the rate of oxidation,  $R_{inh}$ . Judging from the  $t_{inh}$  and  $R_{inh}$  values, it can be said that 2-aminophenols with alkyl and phenyl groups at the 4-position and 2-aminophenols with di-alkyl groups at 4- and 6-positions act as effective radical scavengers.

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