[Regular Paper]

Promoters for Tocopherols as Antioxidants

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Many kinds of additives are used to prevent the degradation of organic chemicals, including macromolecular materials. Tocopherols are natural products known to be effective antioxidants. Now, on the basis of the antioxidation mechanism of tocopherols proposed by us, we have studied amines as promoters, which may enhance the antioxidant activity of a tocopherol, and studied 4-*n*-butoxyphenol, too, as model compounds as tocopherols. It was found that amines exhibit an antagonism to 4-alkylphenols, such as 2,6-di-*t*-butyl-4-methylphenol, whereas they exhibit certain synergism to 4-alkoxyphenols. In addition, it is clarified that an amine having a low ionization potential improves the antioxidant activity of α-tocopherol.

Keywords

Electron transfer, Antioxidant, Tocopherol, Oxyphenol, Amine

1. Introduction

Macromolecular materials and petrochemical products have become very important in modern life. These substances, however, are degraded by autoxidation mainly caused by light, heat, and/or oxygen. Thus, in order to prevent the autoxidation, alkyl and peroxy radicals as chain carriers must be caught as soon as they are formed. A phenolic antioxidant is well known as a peroxy radical scavenger and is added to almost all industrial organic products. A tocopherol having a chroman ring is one such antioxidant derived from natural resources, and is used safely for medical products and cosmetics, as well as foods.

Many researchers pay attention to tocopherols and report their antioxidant effect[1)~6)]. Above all, Ingold *et al*. investigated the effect dynamically and reported the very high antioxidant activity[1)~3)]. They also proposed that the activity comes from a special interaction of a tocopheroxy radical electron with a lone pair on the *p*-oxygen[2)]. However, this proposal cannot explain the reason why 4-methoxyphenol, having no *p*-oxygen contained in a ring structure, shows high activity[7)]. In contrast, our study found a *p*-oxygen substituent has two functions: enhancement of phenolic activity by electron donation to the phenolic hydroxy group, and localization and stabilization of the phenoxy radical electron in the *p*-position by the positive inductive effect of *p*-oxygen. Considering other new experimental facts as well, a mechanism for the antioxidant activity of tocopherol was proposed as shown in **Fig. 1**[8)]. The proposal is characterized by a tocopherol that catches no peroxy radical on the *p*-position. Instead, a tocopheroxy radical catches another peroxy radical by transfer of the radical electron localized on the *p*-position. If this action mechanism is correct, therefore, the radical trapping step of a tocopherol should be promoted in the presence of a substrate making the electron transfer easier. We call this kind of substrate a promoter.

The present study assumed that such a substrate must contain an atom with electronegativity intermediate between those of carbon and oxygen to facilitate electron transfer and to improve the antioxidant activity. Therefore, amines were selected as promoters, which have electronegativities matching the required conditions. This paper will report the effect of amines as promoters.

2. Experiment

2. 1. Reagents

Chlorobenzene was used after distillation as a solvent. The AIBN (2,2'-azobisisobutyronitrile) as initiator was also used after recrystallization of a commercial chemical from methanol. Styrene as substrate was refined by a trap-to-trap method just before use. The BHT (2,6-di-*t*-butyl-4-methylphenol) and 4-*n*-butoxyphenol as phenolic antioxidant were obtained by recrystallization of commercial chemicals, and α-tocopherol was used without any purification. Amines

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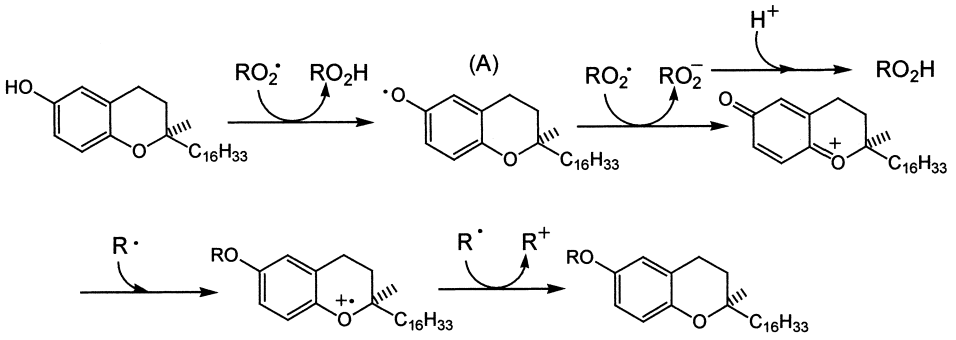


Fig. 1 Proposed Antioxidant Mechanism of Tocopherol

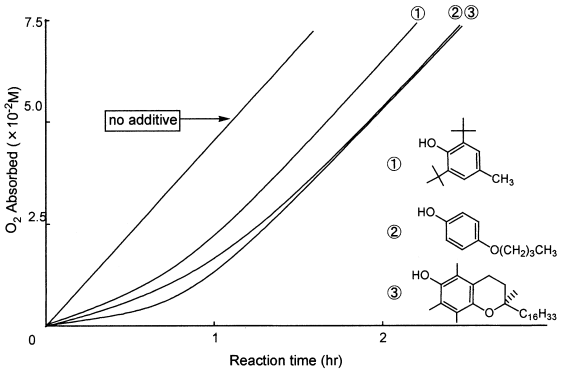
as promoters were commercial chemicals, and only solid amines were purified by recrystallization.

2. 2. Oxidation

Autoxidation of styrene was carried out, using a gas-liquid contact and air-tight reaction system. The temperature was 50°C. Styrene, AIBN, and phenol, if used, were dissolved in chlorobenzene, and the mixture (5 m*l*) was charged into a flask. The flask was attached to a reaction system, which included a transducer DD200 (Toyoda Machine Works, Ltd.) to measure the quantity of oxygen absorbed. To minimize the errors in kinetic results, BHT was always used as a standard phenol.

2. 3. Ionization Potential

WIN MOPAC Version 2.0 (Fujitsu, Ltd.) was used to calculate ionization potentials of amines[9]. The PM3 Method and Geometry Optimization Calculation Type were adopted.



[styrene] = 2.0 M, [AIBN] = 1.0×10^{-2} M, [BHT] = 5.0×10^{-5} M, [4-*n*-butoxyphenol] = 5.0×10^{-5} M, [α-tocopherol] = 5.0×10^{-5} M, 50°C.

Fig. 2 Autoxidation of Styrene in Chlorobenzene

3. Results and Discussion

3. 1. Improvement in Antioxidant Ability of α-Tocopherol by Amine

An autoxidation reaction in the presence of a phenolic antioxidant is expressed by steps (1)-(5).

$$\mathrm{RH} \xrightarrow{Ri} \mathrm{R}\cdot \quad (1)$$

$$\mathrm{R}\cdot + \mathrm{O_2} \xrightarrow{k} \mathrm{RO_2}\cdot \quad (2)$$

$$\mathrm{RO_2}\cdot + \mathrm{RH} \xrightarrow{k_p} \mathrm{RO_2H} + \mathrm{R}\cdot \quad (3)$$

$$\mathrm{RO_2}\cdot + \mathrm{AH} \xrightarrow{nk_{inh}} \mathrm{RO_2H} + \mathrm{A}\cdot \quad (4)$$

$$\mathrm{A}\cdot + \mathrm{RO_2}\cdot \longrightarrow \mathrm{RO_2A} \quad (5)$$

These steps give the rate equation (6) of oxygen absorption in a stationary state:

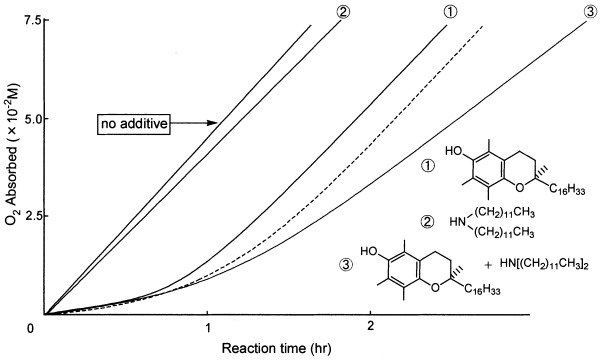
$$\left(-\frac{\mathrm{d[O_2]}}{\mathrm{d}t}\right)_{inh} = \frac{Rik_p[\mathrm{RH}]}{nk_{inh}[\mathrm{AH}]} + Ri \quad (6)$$

In this expression, n denotes the number of radicals trapped by a phenolic moiety, and k_{inh} represents the radical-trapping rate constant. If both n and k_{inh} are high, the phenol is recognized as an excellent antioxidant. However, tocopherols obey the rate equation (7), instead of Eq. (6)[8]:

$$\left(-\frac{\mathrm{d[O_2]}}{\mathrm{d}t}\right)_{inh} \propto \frac{[\mathrm{RH}]^{0.50}[\mathrm{O_2}]^{0.43}Ri^{1.0}}{[\mathrm{AH}]^{1.0}} \quad (7)$$

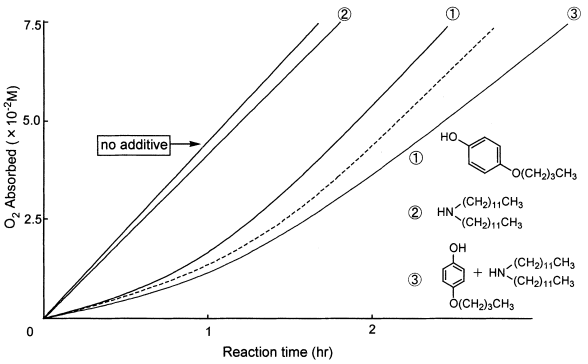
The activity of a tocopherol, therefore, should be discussed, based on Eq. (7), but kinetic constants, such as n and k_{inh}, were not determined precisely. Even if the exact kinetic constants were gotten, however, we could not easily compare the rate constants of phenols with each other, in the case of different rate equations. In this study, therefore, antioxidant activities of phenols are discussed using n and k_{inh} values, derived from Eq. (6), which will be used with little problem for relative evaluation of phenolic antioxidants.

Shown in **Fig. 2** is the amount of oxygen absorbed in the presence of BHT ① or α-tocopherol ③. The initial suppression of oxygen absorption for a longer time indicates higher antioxidant activity. Generally a tocopherol traps one peroxy radical to form a tocopheroxy radical, which is stabilized by resonance, and exhibits higher activity than BHT, due to the relatively stronger electron-donating group on *para* posi-



[styrene] = 2.0 M, [AIBN] = 1.0×10^{-2} M, [α-tocopherol] = 5.0×10^{-5} M, [didodecylamine] = 5.0×10^{-5} M, 50°C.

Fig. 3 Effect of Modifier on Autoxidation of Styrene in the Presence of α-Tocopherol



[styrene] = 2.0 M, [AIBN] = 1.0×10^{-2} M, [4-*n*-butoxyphenol] = 5.0×10^{-5} M, [didodecylamine] = 5.0×10^{-5} M, 50°C.

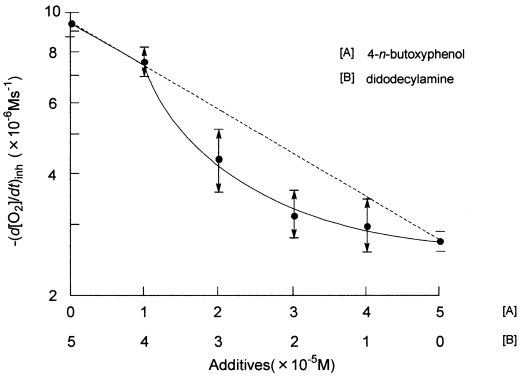
Fig. 4 Effect of Promoter on Autoxidation of Styrene in the Presence of 4-*n*-Butoxyphenol

tion. On the other hand, 4-*n*-butoxyphenol ② was weaker activity than tocopherol, but higher activity than BHT, despite having no substituents on *o*-positions.

Antioxidant activity of α-tocopherol together with the same concentration of didodecylamine is shown in **Fig. 3**. The curve ② shows that didodecylamine itself has a little antioxidant activity, but the coexistence of α-tocopherol and didodecylamine achieves greater suppression of oxygen absorption more for a longer time, in spite of a similar suppression in the initial stage. Shown also in **Fig. 3** is the arithmetic sum curve of ① and ② in a broken line for comparison. When curve ③ is compared with the sum curve the coexistence of α-tocopherol and didodecylamine controls the oxidation better. This result means that didodecylamine is a promoter enhancing the activity of α-tocopherol. In general, the oxygen absorption rate in the presence of an antioxidant should recover the rate obtained in the absence, in a stationary state after complete consumption of the antioxidant. Thus, curve ③ would be expected to regain similar gradient to that of ② in a later stage of oxidation. However, the real final gradient (see, curve ③) is much lower than that of ②. These results suggest that a tocopherol controls oxidation synergistically with didodecylamine.

3. 2. Activity of Model Compound in Presence of Amine

4-*n*-Butoxyphenol was chosen as a model compound of α-tocopherol: it does not have substituents on *o*-positions and a chroman ring structure, but a *p*-oxy substituent. The antioxidant activity is shown in **Fig. 4**. Curves ① and ② are for 4-*n*-butoxyphenol and didodecylamine, respectively, and curve ③ shows the antioxidant activity when both additives coexist. As is observed for α-tocopherol in **Fig. 3**, curve ③ clearly shows that 4-*n*-butoxyphenol, together with didodecylamine, suppresses oxygen absorption much more than

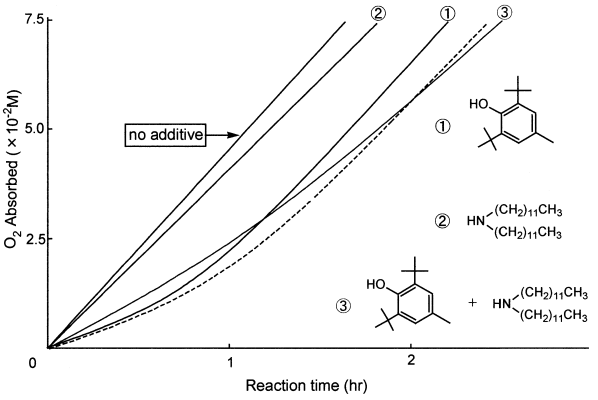


[styrene] = 2.0 M, [AIBN] = 1.0×10^{-2} M, [O_2] = 1.0×10^{-3} M in chlorobenzene at 50°C.

Fig. 5 Relationship between Amount of Additives and Oxygen Absorption Rate

only 4-*n*-butoxyphenol. This result resembles the case of α-tocopherol. **Figure 4** also shows the arithmetic sum curve of ① and ② in a broken line. Comparing curve ③ with the broken line curve, we found both phenol and amine to work synergistically. Interestingly, furthermore, the antioxidant activity of 4-*n*-butoxyphenol was not lost for a long time in the presence of the amine: 30% suppression of oxygen absorption rate was observed, compared with that obtained without any additives, even after the reaction of 4 h, although 4-*n*-butoxyphenol must be consumed completely within 40 min, as judged from curve ①. Thus, such a synergistic interaction of 4-*n*-butoxyphenol with didodecylamine was examined in more detail.

Shown in **Fig. 5** is the oxidation rate obtained by changing relative concentrations of both 4-*n*-butoxyphenol and didodecylamine and keeping the total concentration constant (5.0×10^{-5} M). The arrows



[styrene] = 2.0 M, [AIBN] = 1.0×10^{-2} M, [BHT] = 5.0×10^{-5} M [didodecylamine] = 5.0×10^{-5} M, 50°C.

Fig. 6 Effect of Promoter on Autoxidation of Styrene in the Presence of BHT

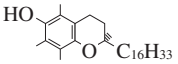
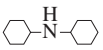
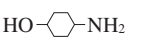
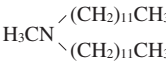
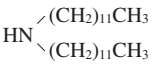
and bars show ranges including about 90% of experimental data. Such a fluctuation was also observed in the case of α-tocopherol. The broken line, as generally accepted, shows an arithmetic mean of oxygen absorption rates, which is obtained by linking two oxygen absorption rates for didodecylamine and 4-*n*-butoxyphenol, respectively, meaning no interaction of both additives, and a solid line shows actual measurement. The result shown in **Fig. 5**, thus, suggests a synergistic interaction of both additives. No effect of didodecylamine could be observed at a concentration ratio of phenol to amine of 1 : 4. This may be ascribed to an insufficient concentration of the phenol to provide a synergistic interaction with didodecylamine. The activity of phenol, in fact, is improved markedly with an increase in its concentration. The oxygen absorption rate is really suppressed in the presence of phenol above 2 : 3 to amine, due to the sufficient phenol. Thus, amine is an effective promoter for the control of oxygen absorption rate. The synergism is observed clearly in the concentration ratio of phenol to amine of 2 : 3 to 3 : 2.

3. 3. Activity of BHT in Presence of Amine

Didodecylamine promoted the antioxidant activity of a phenol with an oxygen atom on *para* position. Then another type of a phenol, such as BHT, was investigated in terms of such an effect of amine. **Figure 6** shows oxygen absorption curves: curves ① and ② show those for BHT and didodecylamine, respectively, and curve ③, for a mixture of both additives. Paying attention in the early stage of oxidation, a combination of BHT and didodecylamine is found to increase the oxygen absorption rate, compared with only BHT. This fact suggests the antagonism of the amine with BHT. Comparing curve ③ with the sum curve shown as a broken line shows this clearly.

On summarizing the above-mentioned results, didodecylamine is found effective for the increase in the antioxidant activity of 4-oxyphenols, but not for the others. In the case of the combination of BHT with didodecylamine, however, the oxidation rate did not regain the rate obtained without any additive, and the oxygen absorption rate was suppressed by approximately 28% even after 4 h, when all additives are estimated to have been consumed completely. This may suggest that didodecylamine has some action besides the above-mentioned antagonism. More data will be necessary to make it clear.

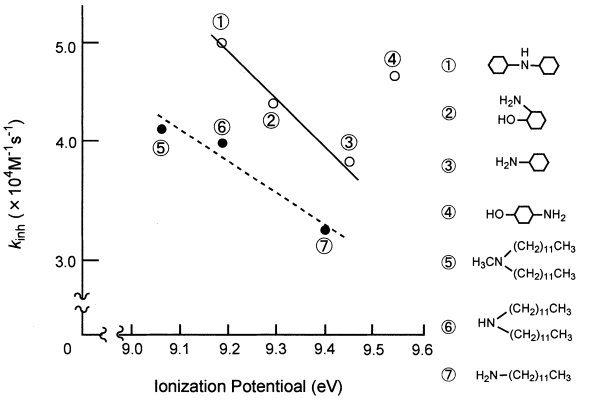
Table 1 Effect of Promoter on Activity of α-Tocopherol

	Ionization potential [ev]	k_{inh} [$\times 10^4$ M^{-1} s^{-1}]	n
		2.2	2.3
① 	9.18	5.0	2.5
② 	9.29	4.4	3.0
③ 	9.45	3.9	2.3
④ 	9.54	4.6	2.5
⑤ 	9.07	4.1	2.2
⑥ 	9.19	4.0	2.2
⑦ $H_2N-(CH_2)_{11}CH_3$	9.40	3.2	2.3

[α-tocopherol] = 2.0×10^{-5} M, [promoter] = 6.0×10^{-5} M, [styrene] = 2.0 M, [AIBN] = 1.0×10^{-2} M, [O_2] = 1.0×10^{-3} M in chlorobenzene at 50°C.
"*n*" and "k_{inh}" as in Eq. (6).

3. 4. Effect of Promoters

Didodecylamine is found to be a promoter for 4-oxyphenols, as expected assuming that an amine may improve or increase the activity of the phenol as an intermediary of electron transfer. Amines with different ionization potentials were examined for synergism with α-tocopherol as summarized in **Table 1**. When kinetic values of *n* and k_{inh} are compared between presence and absence of amines, no remarkable difference is observed with respect to *n* values. The k_{inh} values in the presence of amines, however, are approximately twice as high as that of only α-tocopherol. Interestingly, the k_{inh} values are found to correlate with ionization potentials of amines. In **Fig. 7**, amines ①-④ have ring structures and amines ⑤-⑦ are acyclic amines. Clearly, cyclic and acyclic amines have different activities. Higher k_{inh} values, however, were associated with lower ionization potentials within the series of amines. Ionization potential is a measure of the ease of release of electrons. Now, why the effect is different for various chemical structures of amines



[α-tocopherol] = 2.0×10^{-5} M, [promoter] = 6.0×10^{-5} M, [styrene] = 2.0 M, [AIBN] = 1.0×10^{-2} M, [O_2] = 1.0×10^{-3} M in chlorobenzene at 50°C.

Fig. 7 Relationship between k_{inh} and Ionization Potential of Promoter

and why the activity of 4-hydroxylcyclohexylamine ④ is completely different from those of other amines cannot be explained, but **Fig. 7** supports the idea that an amine promotes the antioxidant activity of 4-oxyphenol through electron transfer.

4. Conclusion

The reaction mechanism shown in **Fig. 8** is proposed on the basis of the results of this study and the action mechanism of tocopherol to convert a peroxy radical into peroxy anion by electron transfer (**Fig. 1**). The amino group of an amine donates an electron to the peroxy radical through route (a) to form the radical cation. Route (a) is considered reversible, because an aliphatic amine, in general, does not trap a peroxy radical so easily. If the radical cation easily accepts an radical from a tocopheroxy radical (route (b)), the forward reaction of route (a) will proceed without difficulty. In **Fig. 1**, the faster conversion of a tocopheroxy radical (A) into a quinoid cation (B) should make the formation of (A) faster. As a result, the k_{inh} value will be increased in the presence of an amine, especially, an amine with a low ionization potential. This result supports the antioxidant mechanism for tocopherol proposed previously[8].

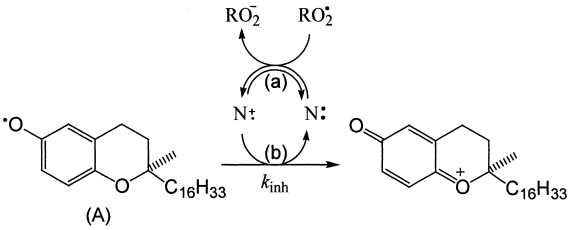


Fig. 8 Action Mechanism of Promoter

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要　　旨

トコフェロールの酸化防止能向上剤

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高分子化合物を含めた化学製品には長寿命化のために様々な添加剤が用いられている。その一つであるトコフェロールは非常に優れた酸化防止効果を持つ天然系物質として知られている。以前我々の提案したトコフェロールの作用機構を基に，トコフェロールの酸化防止活性を向上させる活性化助剤として可能性があるアミンを検討した。検討はトコフェロールだけでなくそのモデル化合物として 4-*n*-ブトキシフェノールを用いて行った。その結果，アミンは 2,6-ジ-*t*-ブチル-4-メチルフェノールと拮抗(きっこう)作用を示したが，4-アルコキシフェノールとは明らかな相乗効果を示した。さらに，イオン化ポテンシャルが小さいアミンはトコフェロールの酸化防止活性を向上させることを明らかにし，アミンの作用機構を推定した。