[Regular Paper]

Cinnamic Acid Derivatives (Part 1)
Proposal as New Phenolic Antioxidants

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Cinnamic acid derivatives, especially esters, were examined as antioxidant in the autoxidation of styrene initiated by azo-bis-isobutyronitrile. A few *o*-hydroxy-cinnamic acid esters exhibited superior activities of antioxidants to 2,6-di-*tert*-butyl-4-methylphenol (BHT) which often is used as a standard substrate of phenolic antioxidants. In some cases, the rate constant k_{inh} of a reaction between the ester and peroxy radicals was remarkably higher, for example, about 6 times higher than that of BHT. It was also found, furthermore, that the ester can arrest about four peroxy radicals, notwithstanding that BHT can trap, at highest, only two peroxy radicals. The alcoholic moiety of the ester little affected directly the activity as antioxidant, but the moiety provided a possibility to function as a light absorber similar to the one of benzophenone-type.

1. Introduction

Organic substrates or materials, such as plastics, resins, petroleum products, etc., are used under atmospheric circumstances, and thus are exposed to harmful oxygen leading to degradations by oxidation. To prevent the degradation, phenolic antioxidants are widely used in many fields¹⁾. From the standpoint of structural characteristics of popular antioxidants for plastics, they can be classified mainly into three categories containing following phenolic moieties:

These structures have the respective characteristics, which are utilized well in respective suitable fields. Fundamentally, it is known that electron-donating substituents accelerate the reaction with peroxy radicals²⁾, and bulky substituents on ortho- and para-positions make sure of trapping nearly two peroxy radicals per phenolic moiety³⁾.

In nature, oxygen can harm biobody, while it is most important for the vital action of aerobic organisms. Oxygen can easily attack, for example, lipids constituting a biomembrane, and

ultimately degrade or break the cells themselves. A biobody contains antioxidants which prevent such degradation. Tocopherols are representative antioxidants found in almost all kinds of living things^{1),4)}. Other phenolic antioxidants, which are characteristic of specific living things, are also discovered. Caffeic acid, 3,4-dihydroxy cinnamic acid, for example, exist in coffee beans and, recently, caffeic acid and its analogues have been reported⁵⁾ to be much more effective antioxidants than phenols synthesized so far.

The authors supposed that the activity of a caffeic acid is derived from an olefinic group conjugated with a phenyl group, and prepared cinnamic acid derivatives, and examined their activities as antioxidants. As a result, it was found that some cinnamic acid derivatives are surprisingly effective antioxidants. Thus, some of the derivatives are nominated as new antioxidants, which are not included in above-mentioned categories.

2. Experimental

2.1. Materials

Cinnamic acid derivatives were synthesized as follows:

a) (2-Hydroxy-4-methyl)-phenyl *o*-hydroxy-cinnamate
o-Hydroxy-cinnamic acid (1.64 g, 0.01 mol) and homocatechol (3.72 g, 0.03 mol) were dissolved in tetrahydrofuran (25 ml), to which conc. sulfuric

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acid (5 ml) was added. The mixture was refluxed for 4 h. After the completion of reaction, the solvent was removed in vacuum. Diethyl ether was added to the concentrated residue and sulfuric acid was removed completely by washing with water. Then the diethyl ether layer was dried over anhydrous sodium sulfate, and the solvent was distilled off. The resulting oily material was triturated with hexane (5 ml), and then was homogenized by adding the least amount of methylene chloride. The mixture was left overnight at room temperature. The precipitated white crystal was separated, and was recrystallized from benzene.

Yield: 0.31 g (11.5% based on *o*-hydroxy-cinnamic acid)

Mp: 179.5-180.5°C

Analysis: $C_{16}H_{14}O_4$ (270.3)

calcd. C 71.10%; H 5.18%

found C 70.94%; H 5.07%

IR (KBr) (cm^{-1}): 3300 (–OH), 2970 (–CH₃), 1750 (C=O), 1620 and 970 (trans-olefin), 1200 (phenolic OH), and 760 and 690 (*o*-substituted benzene)

H-NMR ($CHCl_3$) (δ , ppm): 2.15 (–CH₃, s, 3H), 6.30 and 6.66 (olefinic protons, 2H), and 6.94-7.56 (phenyls, m, 7).

b) Phenyl *o*-hydroxy-cinnamate

The subject compound was prepared according to the same procedure as mentioned in the paragraph a), except that *o*-hydroxy-cinnamic acid (4.92 g, 0.03 mol), phenol (8.46 g, 0.06 mol), and sulfuric acid (15 ml) were used.

Yield: 0.36 g (5.0% based on *o*-hydroxy-cinnamic acid)

Mp: 119.0-121.0°C

Analysis: $C_{16}H_{15}O_3$ (238.2)

calcd. C 75.00%; H 5.00%

found C 75.16%; H 4.96%

IR (KBr) (cm^{-1}): 3300 (–OH), 2920 (–CH₂–), 1750 (C=O), 1620 and 970 (trans-olefin), 1200 (phenolic OH), and 760 and 690 (*o*-substituted benzene)

H-NMR ($CHCl_3$) (δ , ppm): 4.45 (olefinic protons, 2H), and 6.94-7.56 (phenyls, m, 9).

c) 2-Hydroxy-phenyl *o*-hydroxy-cinnamate

The subject compound was prepared according to the same procedure as mentioned in paragraph a), except that *o*-hydroxy-cinnamic acid (1.64 g, 0.01 mol) and catechol (3.30 g, 0.03 mol) were used.

Yield: 1.36 g (53.0% based on *o*-hydroxy-cinnamic

acid)

Mp: 155.0-157.0°C

Analysis: $C_{15}H_{11}O_4$ (255.3)

calcd. C 70.03%; H 5.05%

found C 70.58%; H 4.79%

IR (KBr) (cm^{-1}): 3400 (–OH), 2910 (–CH₂–), 1750 (C=O), 1620 and 970 (trans-olefin), 1200 (phenolic OH), and 760 and 690 (*o*-substituted benzene)

H-NMR ($CHCl_3$) (δ , ppm): 4.45 (olefinic protons, 2H), and 6.94-7.56 (phenyls, m, 8).

d) Phenyl cinnamate

The subject compound was prepared according to the same procedure as mentioned in paragraph a), except that cinnamic acid (4.44 g, 0.03 mol) and phenol (0.94 g, 0.03 mol) were used.

Yield: 1.68 g (25.0% based on cinnamic acid)

Mp: 92.7-94.3°C

Analysis: $C_{16}H_{12}O_2$ (212.3)

calcd. C 80.35%; H 5.35%

found C 80.12%; H 5.10%

IR (KBr) (cm^{-1}): 2970 (–CH₂–), 1750 (C=O), 1640 and 970 (trans-olefin), and 760 and 690 (*o*-substituted benzene)

H-NMR ($CHCl_3$) (δ , ppm): 4.45 (olefinic protons, 2H), and 6.94-7.56 (phenyls, m, 10).

e) 2-Hydroxy-phenyl cinnamate

The subject compound was prepared according to the same procedure as mentioned in paragraph a), except that cinnamic acid (1.48 g, 0.01 mol) and catechol (3.30 g, 0.03 mol) were used.

Yield: 1.20 g (16.7% based on *o*-hydroxy-cinnamic acid)

Mp: 89.5-90.0°C

Analysis: $C_{15}H_{13}O_3$ (229.3)

calcd. C 75.00%; H 5.00%

found C 75.21%; H 4.81%

IR (KBr) (cm^{-1}): 3300 (–OH), 1710 (C=O), 1640 and 970 (trans-olefin), 1180 (phenolic OH), and 760 and 690 (*o*-substituted benzene)

H-NMR ($CHCl_3$) (δ , ppm): 4.45 (olefinic protons, 2H), and 6.94-7.56 (phenyls, m, 9).

Other reagents, such as 2,6-di-*tert*-butyl-4-methyl-phenol (BHT), styrene, azo-bis-isobutyronitrile (AIBN), and chlorobenzene were commercial products, and used after conducting conventional purifications.

2. 2. Procedure

A flask was charged with a phenolic antioxidant, styrene, AIBN, and chlorobenzene, and was purged completely with oxygen by bubbling for 15 min.

The flask was set and connected to a transducer, and the reaction was allowed to start and proceed at the temperature of 50°C. The amount and rate of oxygen absorbed were calculated from electrically recorded change of pressure in a closed reaction system.

3. Results and Discussion

Shown in **Fig. 1** is the amount of oxygen uptaken in the presence of a cinnamic acid ester. The figure includes such a result obtained in the presence of BHT for comparison. In the case where no antioxidant is present in an autoxidation system, the oxidation proceeds smoothly at a considerably high rate. The addition of BHT as standard antioxidant, however, lowered remarkably the reaction velocity. New types of antioxidants, cinnamic acid esters, synthesized by the authors, on the other hand, showed antioxidative activities, depending on the position of phenolic hydroxyl groups. Only one hydroxyl on the ortho position of phenyl of an alcoholic component did not seem effective as an oxidation inhibitor (the Ester (C)), while the hydroxyl of cinnamic acid exhibited oxidation-inhibiting activity comparable to, or rather higher than, that of BHT during the incipient period of reaction (the Ester (B)). Furthermore, co-existence of both hydroxyls showed an eminently excellent ability to inhibit the oxidation (the Ester (D)).

In general, autoxidation proceeds in the presence of a phenolic antioxidant according to the following steps:

where InhH represents a phenolic antioxidant. In this case, the rate of oxygen absorptions is described as

$$-\frac{d[\text{O}_2]}{dt} = \frac{k_p[\text{RH}]R_i}{n k_{\text{inh}}[\text{InhH}]} + R_i$$

The rate constant, k_{inh} , directly corresponds to the rate of oxygen absorption during inhibited period and R_i means the rate of initiation. The value n ,

[Styrene]=2.0 M, [AIBN]= 10^{-2} M, [additive]= 10^{-4} M.

Fig. 1 Autoxidation of Styrene in Chlorobenzene under Diffused Light at 50°C

on the other hand, represents the number of peroxy radicals trapped per phenolic moiety, and is calculated from an inhibited period, namely an induction period. When a phenolic antioxidant traps a peroxy radical, the resulting phenoxy radical is in resonance forms, as shown in **Scheme 1**. One of radicals in such forms, for example, can react with another peroxy radical, but sometimes react with the other phenoxy radical, especially when it has no bulky substituents on ortho and/or para positions. In the former case, two peroxy radicals are trapped by a phenolic antioxidant (namely $n=2$), while the latter case gives only $n=1$. Thus, in general, the n value ranges from one to two. Referring to **Fig. 1**

Table 1 Antioxidative Activity of Cinnamic Acid Derivatives

Run	Additive	$(-d[O_2]/dt)_{inh} [\times 10^{-7} \text{ Ms}^{-1}]$	$k_{inh} [\times 10^4 \text{ M}^{-1}\text{s}^{-1}]$	Induction period [min]	n [mol]
1	none	25.0	—	0	0
2		13.8	1.6	60	2
3	(A)	25.0	—	2.4	0.1
4	(B)	2.8	3.8	122	4.1
5	(C)	24.0	—	4.8	0.2
6	(D)	1.6	6.3	130	4.4
7	(E)	1.0	10	152	4.4

50°C; [styrene]=2.0 M, [AIBN]= 10^{-2} M, [additives]= 10^{-4} M.

again, a cinnamic acid ester, having a phenolic hydroxyl on the ortho-position of phenyl of the acid residue, such as Ester (D), showed an induction period twice longer than that of BHT, together with a stronger inhibitive action, namely a higher k_{inh} . This is a surprising fact which cannot be explained by the theoretical consideration that a phenolic antioxidant has the n value of at highest 2 and the experimental observation that the increase in k_{inh} results in the decrease in n value³⁾. Thus, such cinnamic acid esters can be nominated as a new type of effective phenolic antioxidants.

Shown in Table 1 are kinetical data for several cinnamic acid esters including BHT. The data are calculated on the assumption that the inhibitive process would follow the above-mentioned elementary steps, although the assumption might not be accepted, because the $n > 2$ can not be explained by such trapping steps of peroxy radicals. In the Table, the cinnamic acid ester (A) showed little or no antioxidative activity, as understood by the comparison with the date obtained in the absence of any additive. This suggests that an olefinic moiety of the compound does not contribute to trapping of peroxy radicals. The Ester (B) decreased the rate of oxygen absorption from $25 \times 10^{-7} \text{ Ms}^{-1}$ (run 1) to $2.8 \times 10^{-7} \text{ Ms}^{-1}$, and furthermore gave the induction period of

122 min. The value n , therefore, was calculated as 4.1. As mentioned before, the Ester (C) showed little or no antioxidative action, in spite of the presence of a phenolic hydroxyl group. This fact means that the hydroxylic hydrogen can form a hydrogen bond with the carbonyl of ester and consequently cannot be easily abstracted by a peroxy radical. The Ester (D) decreased the rate of oxygen absorption to $1.6 \times 10^{-7} \text{ Ms}^{-1}$ and lengthened the induction period to 130 min, giving $n = 4.36$. This dramatically increased activity was more enhanced by the introduction of a methyl group on the phenyl of an alcoholic moiety (the Ester (E)). The above-mentioned results clearly suggest that new antioxidants synthesized by authors need the structure:

as fundamental structure, although the hydroxyl of an alcoholic component seems a little to work synergistically with that of an acid component.

It was found that the alcoholic component of a cinnamic acid ester has a possibility to be utilized to provide other functions. Figure 2 shows autoxidations of styrene in the presence of the Ester (C) or a commercial light absorber, 2-benzoyl-4-

[Styrene]=2.0 M, [AIBN]= 10^{-2} M, [additive]= 10^{-4} M.

Fig. 2 Autooxidation of Styrene in Chlorobenzene at 50°C

methoxy-phenol. Broken and solid lines illustrate the amounts of oxygen absorption under diffused light and in dark, respectively. The rate of oxidation under diffused light, of course, is a little higher due to co-occurrence of photo-oxidation. When the Ester (C) or the light absorber was added and the autooxidation was carried out under diffused light, the Ester showed a light-absorbing ability and inhibited the oxidation to the approximately same degree as carried out in dark, although this was a little weaker than that of the commercial light absorber. This fact suggests that the alcoholic part can work as light absorber.

As shown in Table 1, the Ester (A) did not show any antioxidative activity, but a Photo-Fries rearrangement was observed by IR spectra (Fig. 3), when one of such esters was exposed to light. That is, in an UV irradiation of phenyl cinnamate (Fig. 3(a)) in benzene, the absorption bands by phenolic hydroxyl appeared at about 3500 and 1200 cm^{-1} , showing the formation of β -(*o*-hydroxybenzoyl)-styrene.

These results imply that an Ester, regardless of the presence or absence of such a hydroxylic group on an alcoholic moiety as provided on the Ester (C), may be utilized as an excellent light absorber.

Illustrated in Fig. 4 is the further evidence of activities given by the Ester (E). When the concentration of the ester was made twice or five times higher than that shown in Table 1 (10^{-4} M), the

Fig. 3 IR Spectra of Photo-Fries Rearrangement of Phenyl Cinnamate

[Styrene]=2.0 M, [AIBN]= 10^{-2} M.

Fig. 4 Autooxidation of Styrene in Chlorobenzene under Diffused Light at 50°C

induction periods became 420 min (about 3.2 times) and 900 min (about 6.8 times), respectively. It is theoretically well known that an induction period is proportional to the concentration of an antioxidant added. This is not likely applied to oxidation inhibitors in the presence of the cinnamic acid ester. This fact cannot be explained easily and exhibits an aspect of complicated

behaviors of the ester as an inhibitor.

Strong inhibitive actions of a few cinnamic acid esters are shown above. Many phenolic antioxidants, which have been used for long time, contain bulkier substituents on both ortho and para positions to prevent the dimerization of phenoxy radicals. Although cinnamic acid esters have no substituent on one ortho position as well as para position, in contrast, they do not seem to be dimerized, as assumed on the basis of considerable high values of n . This is attributed to the localization of an electron, on the olefinic group, of a phenoxy radical, which consequently cannot react with another phenoxy radical due to steric hindrance. This localized radical, thus, may have

a possibility to arrest a peroxy radicals, leading to high n values. This point must be clarified after further detailed experiments.

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要 旨

桂皮酸誘導体（第1報）新しいフェノール系酸化防止剤としての提案

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アゾビスイソブチロニトリルを開始剤とするスチレンの液相自動酸化を行い, 桂皮酸誘導体, 特に桂皮酸のフェノールエステルの酸化防止剤としての可能性を試験した。フェノール性水酸基を全然持たないものは全く酸化防止能を示さず, 桂皮酸のオレフィン性二重結合はラジカル捕そく能のないことが分かった。また, アルコール成分に水酸基を有する桂皮酸 *o*-ヒドロキシフェニルも酸化防止能を全然示さなかった。しかし, いくつかの *o*-ヒドロキシ桂皮酸フェニルは非常に強力な酸化防止能を有し, フェノール系酸化防止剤の基準物質として良く用いられる 2,6-ジ-*tert*-ブチル-4-メチル-フェノール (BHT) よりも良好な酸化防止活性を示した。たとえば, *o*-ヒドロキシ桂皮酸フェニルとパーオキシラジカルとの反応の速度定数 (k_{inh}) は, BHT のそれより約 2.4 倍も高かった。興味あることに, 桂皮酸成分とアルコール成分の両方の *o*-位に水酸基のある場合にはそれが 4 倍も高く, *o*-ヒドロキシ桂皮酸 2-ヒドロキシ-4-メチル-フェニルのそれは 6.3 倍であった。

一般に, フェノール系の酸化防止剤はそのフェノール残基あたり, 理論上たかだか二つのパーオキシラジカルしか捕そくすることができない。これは BHT にも当てはまる。しかし驚くべきことに, *o*-ヒドロキシ桂皮酸エステルは約四つのパーオキシラジカルをも捕そくしうることが発見された。この理由は現在不明であるが, 上述した高い k_{inh} と考え合わせると, *o*-ヒドロキシ桂皮酸エステルは新しい種類のフェノール系酸化防止剤として提案できる。

先に述べたように, 桂皮酸フェニルのアルコール成分は直接ラジカル捕そくに, すなわち酸化防止活性に寄与しないが, その *o*-位に水酸基がある場合には, ベンゾフェノン型と同様な光吸収剤として機能しうることが見い出され, また *o*-位水酸基のない時でも光-Fries 転位によってそのような水酸基が生成するために, 光吸収剤として働く可能性のあることが示唆された。

Keywords

Antioxidant, Additive, Substituted phenyl cinnamate, *o*-Hydroxy cinnamate, Radical scavenger, Photo-stabilizer