New Bifunctional Antioxidants : Intramolecular Synergistic Effects between Benzofuranol and Thiopropionate Group, Part II

NEW BIFUNCTIONAL ANTIOXIDANTS: INTRAMOLECULAR SYNERGISTIC EFFECTS BETWEEN BENZOFURANOL AND THIOPROPIONATE GROUP, PART II

Yu ANDOH*, Masahiro TANAKA*, Tsutomu HIROHASHI*,
Tomoyuki OKAMOTO and Tomihiro NISHIYAMA*

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Abstract

The antioxidant activities of benzofuranols and chromanols with methyl, methyl thiomethyl and thiopropionate groups were evaluated for the oxidation of tetralin at 61 and 140℃. The antioxidants tested showed almost the same behaviour for the oxidation of tetralin initiated by an azo initiator at 61℃. However, benzofuranol and chromanol with a thiopropionate group at the *meta* position of the OH group were shown to improve antioxidant activity at high temperature to a greater extent than the methyl and methyl thiomethyl groups.

1. Introduction

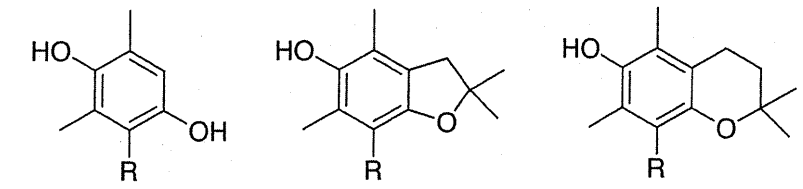
Phenols are widely used as antioxidants for foods, lipids in biological membrances and industrial products, such as plastics, oils and rubber products. For example, α-tocopherol, a component of vitamin E, and 2,6-di-*tert*-butyl-4-methylphenol are known as a natural and a synthetic antioxidants, respectively. The structural characteristics of α-tocopherol is that has a long phytyl side chain, a chroman ring and a phenolic OH group. Burton et al[1,2] reported that the rate constant for H-atom abstraction by peroxyl radicals for α-tocopherol depends on the degree of stabilization of the phenoxyl radical. In turn, stabilization of the phenoxyl radical depends on two factors: (i) the extent of orbital overlap between the 2p-type lone pair of electrons on the *para* oxygen atom and the aromatic π-electron system, and (ii) the electron-donating ability of the group bonded to the *para* oxygen atom. Moreover, Burton et al[2] and other research groups[3,4] have recently reported that the antioxidant activity of 2,3-dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran was 1.8 times larger than that of α-tocopherol. The higher antioxidant activity in this case, as compared to α-tocopherol, was attributed to a better overlap between the non-phenolic oxygen 2p-type lone pair and the aromatic π-system in the 2,3-dihydrobenzofuran.

For the stabilization of polymers, it is customary to use phenolic antioxidants in combination with other stabilizers, and many examples of efficient recipes are used to avoid unwanted degradation during processing and long-term application. For example, the combination of hindered phenols with dilauryl 3,3'-thiodipropionate produce a synergistic

*Department of Applied Chemistry

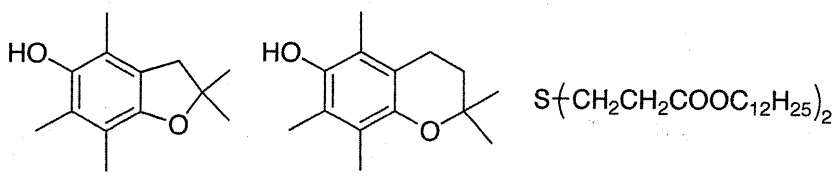
stabilizing effect.[5,6] The latter antioxidant contributes to deactivation of hydroperoxides, ROOH.

In a previous paper, we reported that 2,2,5,7-tetramethyl-6-chromanol with a thiopropionate group in the same molecule acts as a potent antioxidant at high temperature.[7] In this work, the peroxyl-radical-trapping and hydroperoxide-decomposing abilities of 3-(5-hydroxy-2,2,4,6-tetramethyl-2,3-dihydrobenzofuran-7-ylsulfanyl)-propionic acid ethyl ester **2b** is compared with related antioxidants with commercially available 2,2,5,7,8-pentamethyl-6-chromanol (PMC) (Scheme 1).



1 **2** **3**

a: R=CH_2SMe, b: R=SCH_2CH_2COOEt



PMB PMC DT

Scheme 1. Antioxidants used in this study

2. Experimental

2. 1. General

Mass spectra were measured with a Perkin-Elmer model 910 spectrometer operating in the electron impact mode (70 eV). Nuclear magnetic resonance spectra were recorded using a JEOL GSX-400 spectrometer operating at 400 MHz for ^1H and 100.6 MHz for ^{13}C in $CDCl_3$ and chemical shifts are referenced to $(CH_3)_4Si$.

2.2. Assay of antioxidant activity

The rate of oxidation was determined by the volume of oxygen consumption during oxidation. The volume of oxygen consumption was measured as a function of time under 760 Torr (1 Torr = 133.322 Pa) of O_2 with 50.0g of tetralin containing an antioxidant [1 mM] and α, α'-azobisisobutyronitrile (AIBN, [10 mM]) as the initiator. The oxidation temperature was maintained at 61 ± 0.1℃. Thermally-initiated oxidation of tetralin was carried out under 760 Torr of O_2 with 20.0g of tetralin containing an antioxidant [0.39 mM and/or 0.28 mM] at 140 ± 0.1℃. The induction period (t_{inh}) value was determined graphically 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.

Peroxide value (POV) for tetralin was determined by measuring the time required to oxidize tetralin to a given extent by dry oxygen blowing at 140℃. The POV was measured periodically according to the standard method of the Japan Oil Chemists' Society.[8] Hydroperoxide was reduced by adding a potassium iodide aqueous solution to the tetralin solutions and the iodine thus produced was titrated by an aqueous solution of sodium thiosulfate to measure the POV.

2. 3. Materials

3,5-Dimethyl-[2-methylsulfanylmethylbenzene]-1,4-diol (1a). ^{1}H NMR δ =2.04(s, 3H), 2.19(s, 3H), 2.24(s, 3H), 3.81(s, 2H), 4.27(s, 1H), 5.51(s, 1H), 6.55(s, 1H).

3-[3,6-Dihydroxy-2,4-methylsulfanyl]-propionic acid ethyl ester (1b). Mp 57.2-58.3℃. ^{13}C NMR δ =14.2, 14.4, 16.5, 30.5, 34.0, 113.8, 115.1, 127.1, 127.8, 145.8, 151.4, 171.8. ^{1}H NMR δ =1.26(t, J=7.3Hz, 3H), 2.23(s, 3H), 2.44(s, 3H), 2.47(t, J=7.3Hz, 2H), 2.84(t, J=7.3Hz, 2H), 4.13(q, J=7.3Hz, 2H), 6.67(s, 1H).

2,2,4,7-Tetramethyl-[6-ethylsulfanylmethyl]-2,3-dihydrobenzofuran-5-ol (2a). Mp 81.2-82.8℃. ^{13}C NMR δ =11.7, 13.0, 14.9, 28.3, 29.1, 42.7, 85.5, 115.7, 119.5, 121.2, 123.2, 145.5, 151.0. ^{1}H NMR δ =1.43(s, 6H), 2.04(s, 3H), 2.09(s, 3H), 2.21(s, 3H), 2.90(s, 2H), 3.66(s, 2H), 4.31(s, 1H),

3-[5-Hydroxy-2,2,4,6-tetramethyl-2,3-dihydrobenzofuran-7-ylsulfanyl]-propionic acid ethyl ester (2b). Mp 88.5-89.9℃. ^{13}C NMR δ =13.1, 13.7, 14.2, 28.3, 29.2, 34.8, 42.7, 60.5, 86.3, 110.6, 121.6, 124.1, 125.4, 145.8, 154.3, 172.2. ^{1}H NMR δ =1.23(t, J=7.3Hz, 3H), 1.49(s, 6H), 2.12(s, 3H), 2.36(s, 3H), 2.47(t, J=7.3Hz, 2H), 2.95(s, 2H), 3.02(t, J=3.7Hz, 2H), 4.08(q, J=7.3Hz, 2H).

3. Results and Discussion

3.1. Scavenging effect of benzofuranols with a methyl thiomethyl group and related compounds for the peroxidation of tetralin

The phenols examined in this work are divided for convenience into four classes: firstly, 2,6-dimethylhydroquinones **1**; secondly, 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ols **2**; thirdly, 2,2,5,7-tetramethyl-6-chromanols **3**, as shown in Scheme 1; and lastly, PMC and 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol (PMB). The antioxidant activity for compounds **1-3** in series **a** (R=CH_2SCH_3) and related compounds, as measured by the t_{inh} value at 61℃, are shown in Fig. 1. These results indicate that antioxidant activity decreased in the order of **2a**>PMB>**3a**>PMC>**1a**. Compound **1a** with a methyl thiomethyl group did not suppress oxidation. In contrast, benzofuranol **2a** and chromanol **3a** with a methyl thiomethyl group both suppressed the oxidation. By comparing the substituents on the aromatic ring, in the cases of PMB and **2a**, the methyl thiomethyl group *meta* to the phenolic OH group gave a higher t_{inh} value than that in the case of a methyl group. On the other hand, the methyl thiomethyl group in **3a** has reactivities similar to that of PMC with a methyl group.

Ingold et al[2-4] have measured the rate constants k. for H-atom abstraction by peroxyl

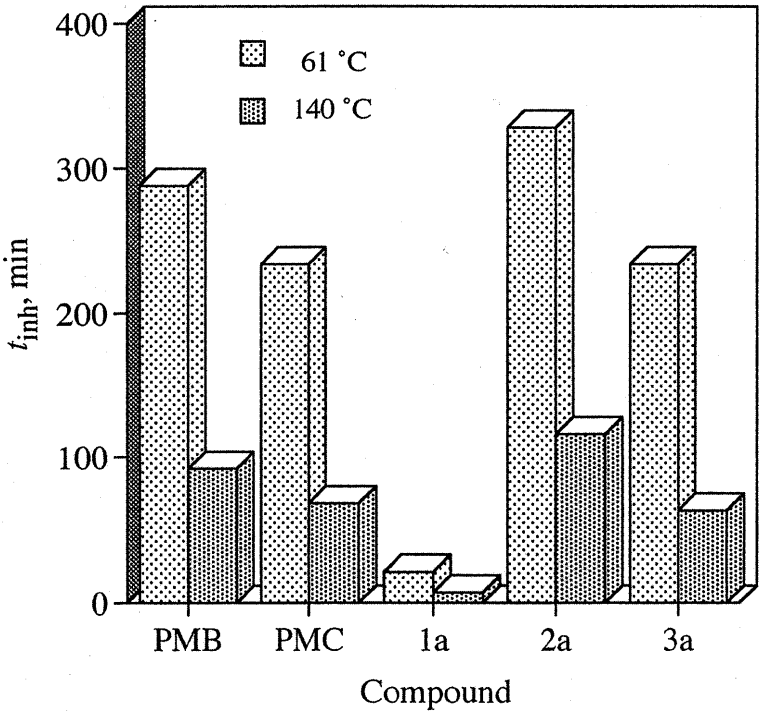


Fig.1 Antioxidant activity of PMB, PMC and its derivatives on the autoxidation of tetralin at 61 and 140℃

radicals from PMC and PMB for the autoxidation of styrene at 30℃. They reported that PMB quenches peroxyl radicals 1.8 times more rapidly than does PMC. This higher antioxidant activity was attributed to a better overlap between the nonphenolic oxygen 2p-type lone pair and the aromatic π-system in PMB, as compared to PMC. However, PMB shows no remarkable increase in antioxidant activity relative to PMC in the peroxidation of tetralin at 61℃. That is, PMB exhibits a t_{inh} value 1.2 times that of PMC.

Scott reported that the t_{inh} values of 3,5-di-*tert*-butyl-4-hydroxybenzyl sulphides were about four times longer than that of 2,6-di-*tert*-butyl-4-methylphenol in the oxidation of decalin at 140℃.[9,10] He suggested that such high activity may be attributed to an additional antioxidant function resulting from the presence of the sulfur atom. On this basis, we measured the antioxidant activity of **1a-3a**, PMC and PMB under thermoxidative conditions at 140℃. Fig. 1 shows the t_{inh} for **1a-3a** [7.5×10^{-6} mol/20.0g tetralin] as measured by O_2 absorption in tetralin at 140℃ and those obtained for PMC and PMB. Neither **1a-3a** nor PMC or PMB give higher values than those at 61℃. That is, the compounds tested caused remarkable lowering in antioxidant activity. There is a 65%～73% reduction in the t_{inh} value, as compared with the values at 61℃. We conclude that the methyl thiomethyl group at the *meta* position relative to the phenolic OH group has no effect on hydroperoxide decomposition under thermoxidative conditions.

3.2. Scavenging effect of benzofuranol with a thiopropionate group and related compounds for the peroxidation of tetralin

The antioxidant activity as measured by the t_{inh}, for **1-3** in series **b** (R=SCH_2CH_2COOEt), and for PMC and PMB are shown in Fig. 2. The antioxidant activities, during inhibition of autoxidation of tetralin at 61℃, for **2b** and **3b** with a thiopropionate group are quite similar to those of **2a** and **3a** with a methyl thiomethyl group. The exception is **1b**. As mentioned in the previous section, compound **1a** did not act as an antioxidant, but **1b** exhibited a moderate activity.

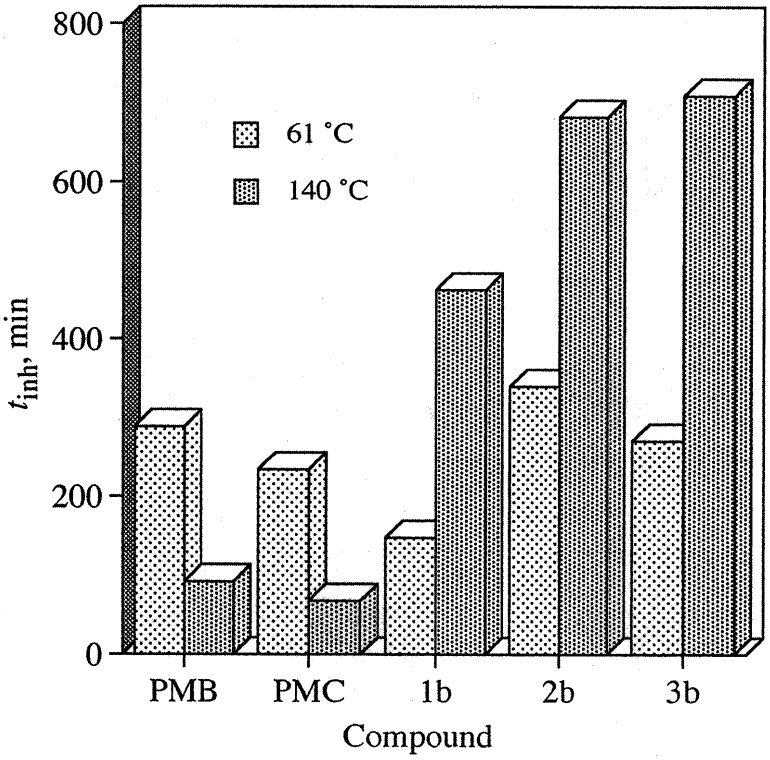


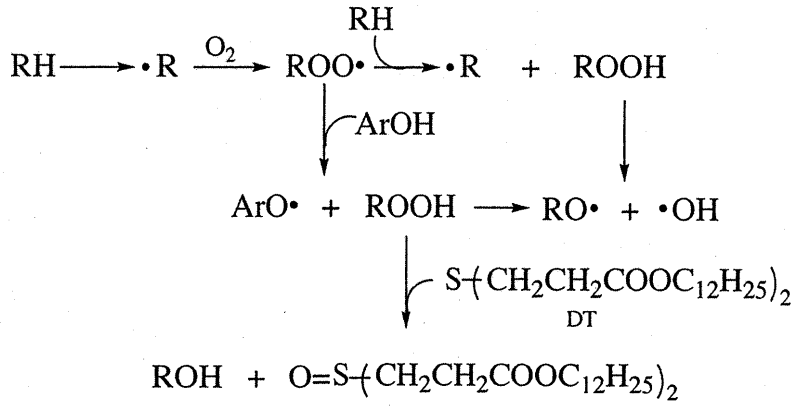
Fig.2 Antioxidant activity of PMB, PMC and its derivatives on the oxidation of tetralin at 61 and 140℃

The antioxidant activities of series **b** at 140℃ show a marked contrast with the results at 61℃. The phenols with a thiopropionate group increase the t_{inh}: compound **1b** by 3.1-fold, **2b** by 2.0-fold, and **3b** by 2.6-fold, as compared with the compounds, **1a**, **2a**, and **3a** with a methyl thiomethyl group, respectively.

At high temperature, the high antioxidant activity in series **b** is obviously due to its thiopropionate group. We can presume that the thiopropionate group scavenged the hydroperoxides produced by the reaction of peroxyl radicals with **1-3**. In other words, it suggests that antioxidants with dual functions in the same molecule produce excellent antioxidant activity. We conclude that phenols with a thiopropionate group in the same molecule, such as **2b** and **3b**, may be effective antioxidants for preventing the oxidation of

oils and fats at high temperature.

Scheme 2 shows the antioxidant and synergistic mechanisms. Generated alkyl radicals(R·) react with oxygen to give peroxyl radicals (ROO·), which promote oxidative degradation. The role of antioxidants, such as phenols (ArOH), is to trap the peroxyl radicals to produce stable phenoxyl radicals (ArO·) and ROOH. However, ROOH will easily decompose to produce another radical species such as RO· and ·OH. The role of thiodipropionate (DT) is to decompose the ROOH to give the stable alcohol (ROH).



Scheme 2. Synergistic mechanism

3.3. Evaluation of peroxide value

Hydroperoxide decomposing ability of PMC and **2-3** for the oxidation of tetralin at 140℃ was evaluated by measuring the time that POV takes to reach 50 and 180 meq/kg (Table 1).

Table 1 Antioxidant activity of PMC derivatives on the autoxidation of tetralin at 140 ℃[a)]

Run	Antioxidant	t_{inh}	POV(min) taken to reach	
		min	50 meq/kg	180 meq/kg
1	**2a**	116	80	265
2	**2b**	682	(902)[b)]	-
3	**3a**	63	75	252
4	**3b**	726	(847)	(1136)
5	PMC	68	(64)	(81)
6	None	0	(11)	(30)

a) Oxidation reactions were carried out in tetralin using 0.39 mM antioxidant, unless otherwise noted. b) The values in parentheses were evaluated using 0.28 mM antioxidant.

The POV of the control increased to 50 meq/kg at 11 min and 180 meq/kg at 30 min. The presence of PMC, **2a** and **3a** delayed the increase in POV in a similar fashion. A striking feature of our data is that the compounds **2b** and **3b** with a thiopropionate group caused a remarkable increase in POV. The values of POV (50 meq/kg) for **2b** and **3b** were respectively 14 and 13 times longer than those of PMC. These results indicate that in terms of the potency of antioxidants there was a good correlation between the t_{inh} and POV values.

In conclusion, the overall efficiency of benzofuranol **2b** and chromanol **3b** with a thiopropionate group in the same molecule causes them to be effective radical scavengers and appropriate hydroperoxide decomposing species in the autoxidation of tetralin at higher temperatures than PMC and PMB.

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