Antioxidant Activity and Oxidation Products of 1,2,3,4- Tetrahydroquinoxalines in Peroxyl Radical Scavenging Reactions, Part I

ANTIOXIDANT ACTIVITY AND OXIDATION PRODUCTS OF 1,2,3,4-TETRAHYDROQUINOXALINES IN PEROXYL RADICAL SCAVENGING REACTIONS, PART II

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Abstract

This paper studies the antioxidant activity of 1,2,3,4-tetrahydroquinolines, 3,4-dihydro-2*H*-benzo[1,4]thiazines and 1,2,3,4-tetrahydroquinoxalines in the inhibition of the peroxidation of tetralin induced by an azo initiator. Neither 1,2,3,4-tetrahydroquinoline nor 3,4-dihydro-2*H*-benzo[1,4]thiazine alone acted as an antioxidant, but when they have an electron-donating group at the *para* position to the NH group, they act as potent antioxidants. On the other hand, 1,2,3,4-tetrahydroquinoxaline on its own showed good antioxidant activity. However, 1,2,3,4-tetrahydroquinoxalines with methyl and methoxy groups in the phenyl ring have reactivities similar to or less than that of unsubstituted 1,2,3,4-tetrahydroquinoxaline. The induction periods of 1,2,3,4-tetrahydroquinoxalines with an alkyl group or phenyl group at the 2-position were all longer than the value for the unsubstituted 1,2,3,4-tetrahydroquinoxaline, except for a compound with a *t*-butyl group. The oxidation of 1,2,3,4-tetrahydroquinoxalines by peroxyl radicals generated from an azo initiator in tetralin or benzene yields quinoxalines and a dimer product of quinoxalines, 6-(1,2,3,4-tetrahydroquinoxalin-1-yl)-quinoxaline.

1. Introduction

Reactive oxygen species are known to cause of oxidative damage to such industrial materials as plastics, oils and rubber products. Therefore, the inhibition of free radical oxidation is very important in the chemical industry for preventing unwanted degradation during processing and long-term use. To avoid uncontrolled autoxidation, various kinds of synthetic phenols and amines with high reactivity are now on the market. For example, hindered phenols[1,2] and *N*-alkyl aromatic amines[3] are used on a large scale as excellent antioxidants and antiozonants. In spite of their great practical importance, the detailed mechanisms of the antioxidant action of phenols[4,5] and aromatic amines[6,7] have been elucidated only recently.

In a previous paper, we reported that 1,2,3,4-tetrahydroquinoxalines are potent chain-breaking antioxidants for the autoxidation of tetralin.[8] In the present study, we compared the inhibitory effects of aromatic cyclic amine derivatives, 1,2,3,4-tetrahydroquinolines, 3,4-

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dihydro-2*H*-benzo[1,4]thiazines, and 1,2,3,4-tetrahydroquinoxalines with commercially available 6-ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (Nonflex AW, Seiko Chemical Co. Ltd, Japan). (see Fig.1) We also examined the oxidation products of 1,2,3,4-tetrahydroquinoxalines in the peroxidation system to investigate the mechanism of antioxidant activity.

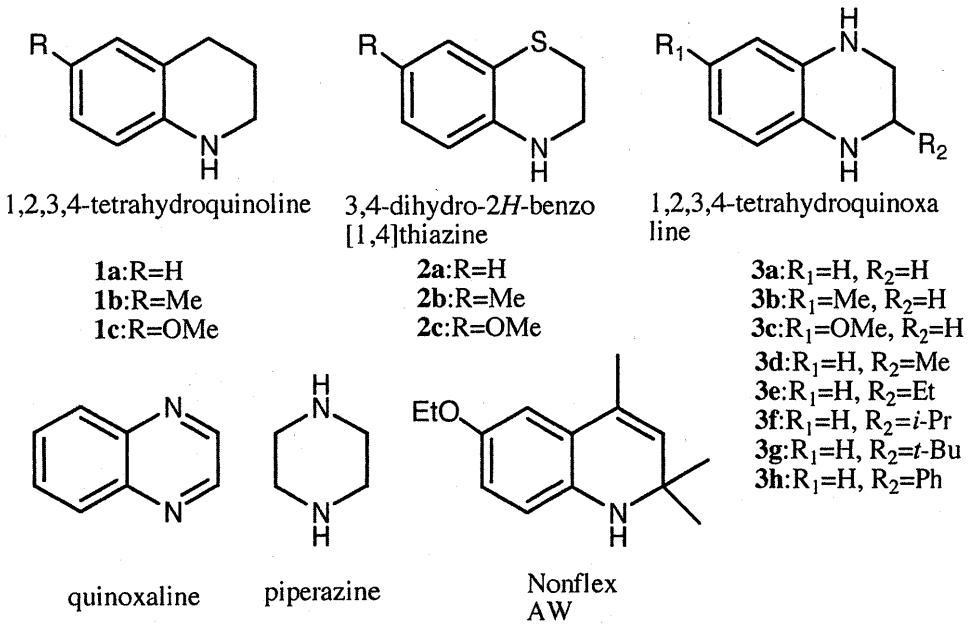


Fig.1 Fused heterocyclic compounds used in this study

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 ^{1}H and 100.6 MHz for ^{13}C in $CDCl_3$ and chemical shifts were 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 50.0 g of tetralin containing an antioxidant (1 mmol dm^{-3}) and α, α'-azobisisobutyronitrile (AIBN, 10 mmol dm^{-3}) as the initiator. The oxidation temperature was maintained at 61 ± 0.1℃. The t_{inh} 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 final uninhibited rates of oxidation.

2.3. Molecular orbital calculations

The bond dissociation energies of the N-H (D(N-H)) and C-H (D(C-H)) bonds were

obtained from the enthalpy of the optimum structures of antioxidants and relative radicals using the techinique of AM1 in WinMOPAC ver.2.0 (Windows), as follows:

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

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

2.4. Materials

Tetralin used for the test was washed with concentrated sulfuric acid, aqueous sodium hydrogen carbonate, and water, then it was dried over anhydrous sodium sulfate and distilled under nitrogen before being used. AIBN was recrystallized from methanol. 1,2,3,4-Tetrahydroquinoline **1a** was obtained from Aldrich. 1,2,3,4-Tetrahydroquinolines **1b** and **1c** are given in Ref. (9) and 1,2,3,4-tetrahydroquinoxalines **3a** and **3d** in Ref. (8). The 3,4-dihydro-2*H*-benzo[1,4]thiazines **2a-2c** were prepared by cyclization reaction from the corresponding *o*-aminobenzenethiols[10] and 1,2-dibromoethane in the presence of KOH in ethanol. The route for the syntheses of **3** is shown in Fig. 2. 6-Substituted quinoxalines were prepared by cyclization reaction from the corresponding 4-substituted *o*-phenylenediamines and glyoxal. The resulting quinoxalines, upon reduction with an $NaBH_4$-$NiCl_2$ system,[11] gave 6-substituted 1,2,3,4-tetrahydroquinoxalines **3b** and **3c**. Similarly, 2-substituted quinoxalines were prepared by cyclization reaction from *o*-phenylenediamine and the corresponding glyoxals. The resulting quinoxalines after reduction, gave 2-substituted 1,2,3,4-tetrahydroquinoxalines **3e-3h**.

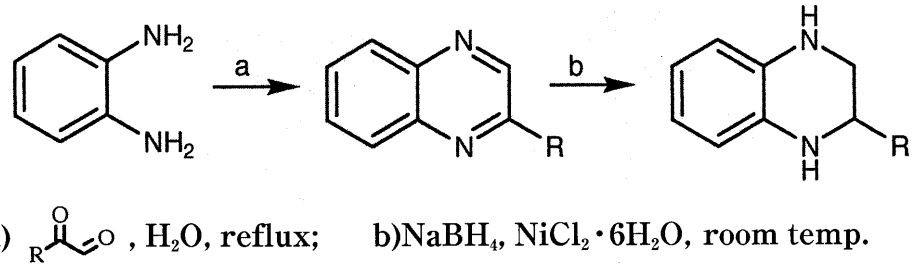


Fig.2 Synthetic route of 1,2,3,4-tetrahydroquinoxalines

3,4-Dihydro-2*H*-benzo[1,4]thiazine (2a). Yield, 35%; Mp, 37.5-39.0℃. ^{13}C NMR δ =26.0, 42.2, 115.3, 115.8, 118.1, 125.5, 127.7, 141.7. ^{1}H NMR δ =3.03-3.05(m, 2H), 3.59-3.62(m, 2H), 6.43-6.45(m, 1H), 6.58-6.62(m, 1H), 6.86-6.87(m, 1H), 6.87-6.89(m, 1H), 6.96-6.98(m, 1H).

7-Methyl-3,4-dihydro-2*H*-benzo[1,4]thiazine (2b). Yield, 67%; Mp, 68.1-69.8℃. ^{13}C NMR δ =20.3, 26.4, 42.3, 115.5, 116.0, 126.1, 127.6, 127.8, 139.3. ^{1}H NMR δ =2.17(s, 3H), 3.07-3.06(m, 2H), 3.56-3.59(m, 2H), 6.36-6.39(m, 1H), 6.68-6.70(m, 1H), 6.80(s, 1H).

7-Methoxy-3,4-dihydro-2*H*-benzo[1,4]thiazine (2c). Yield, 91%; Liquid. ^{13}C NMR δ =26.7, 42.3, 55.7, 111.9, 112.2, 116.8, 117.4, 135.7, 152.3. ^{1}H NMR δ =3.07-3.09(m, 2H), 3.50-3.53(m, 2H), 3.71(s, 3H), 6.42-6.57(m, 3H).

6-Methyl-1,2,3,4-tetrahydroquinoxaline (3b). Yield. 91%; Mp,108.0-109.7℃. ^{13}C NMR δ =20.7, 41.5, 115.1, 115.5, 119.2, 128.6, 130.8, 133.7. ^{1}H NMR δ =2.17(s, 3H), 3.30(br.s, 2H), 3.35-3.43(m, 4H), 6.33-6.44(m, 3H).

6-Methoxy-1,2,3,4-tetrahydroquinoxaline (3c). Yield, 36%; Liquid. ^{13}C NMR δ=41.5, 55.6, 101.1, 103.3, 116.2, 126.7, 135.1, 153.7. ^{1}H NMR δ=3.21(br. s, 2H), 3.31-3.40(m, 4H), 3.70(s, 3H), 6.12-6.17(m, 2H), 6.46-6.49(m, 1H).

2-Ethyl-1,2,3,4-tetrahydroquinoxaline (3e). Mp, 74.1-75.3℃. ^{13}C NMR δ=10.1, 27.1, 46.2, 51.7, 114.4, 118.6, 118.7, 133.4, 133.5, 141.0. ^{1}H NMR δ=1.00(t, J=7.4Hz, 3H), 1.48-1.56(m, 2H), 3.03-3.08(m, 1H), 3.20-3.30(m,1H), 3.36-3.39(m, 1H), 6.49-6.51(m, 2H), 6.57-6.59(m, 2H).

2-*iso*-Propyl-1,2,3,4-tetrahydroquinoxaline (3f). Mp, 79.3-80.9℃. ^{13}C NMR δ=18.6, 18.7, 30.9, 43.9, 55.9, 114.3, 118.3, 118.7, 128.3, 133.3, 133.8. ^{1}H NMR δ=0.97(d, J=6.8Hz, 3H), 1.01(d, J=6.8Hz, 3H), 1.69-1.74(m, 1H), 3.11-3.13(m, 2H), 3.33-3.35(m, 1H), 3.56(br. s, 2H), 6.47-6.50(m, 2H), 6.55-6.58(m, 2H).

2-*tert*-Butyl-1,2,3,4-tetrahydroquinoxaline (3g). Yield, 28%; Mp, 84.5-85.9℃. ^{13}C NMR δ=26.0, 32.7, 42.5, 58.9, 114.2, 114.3, 118.2, 118.7, 133.3, 134.5. ^{1}H NMR δ=1.00(s, 9H), 3.07-3.13(m, 2H), 3.27-3.37(m, 1H), 3.54(br. s, 2H), 6.46-6.59(m, 4H).

2-Phenyl-1,2,3,4-tetrahydroquinoxaline (3h). Yield, 59%; Mp, 79.9-82.1℃. ^{13}C NMR δ=49.1, 54.6, 114.4, 114.8, 118.7, 118.9, 126.9, 127.9, 128.6, 132.6, 134.1, 141.2. ^{1}H NMR δ=3.31(dd, J=8.4, 11.2Hz, 1H), 3.44(dd, J=3.0, 11.2Hz, 1H), 3.71(br. s, 2H), 4.47(dd, J=3.0, 8.4Hz, 1H), 6.55-6.64(m, 4H), 7.29-7.39(m, 5H).

6-(1,2,3,4-Tetrahydroquinoxalin-1-yl)-quinoxaline. Liquid. ^{13}C NMR δ=41.3, 46.9, 115.0, 115.2, 117.4, 119.0, 122.9, 125.9, 128.6, 129.3, 136.2, 139.1, 141.9, 144.5, 144.8, 148.7. ^{1}H NMR δ=3.49(t, J=4.8 Hz, 2H), 3.86(t, J=4.8 Hz, 2H), 6.61-6.66(m, 2H), 6.82-6.85(m, 1H), 7.01-7.10(m, 1H), 7.54-7.55(m, 1H), 7.77-7.79(m, 1H), 7.81-7.93(m, 1H), 8.68(d, J=2.0 Hz, 1H), 8.61(d, J=2.0 Hz, 1H). Found: C, 73.17; H, 5.41; N, 21.41%. Calcd for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36%.

3. Results and Discussion

Data reflecting the antioxidant activities of 1,2,3,4-tetrahydroquinoline **1**, 3,4-dihydro-2*H*-benzo[1,4]thiazine **2**, and 1,2,3,4-tetrahydroquinoxaline **3**, as denoted by t_{inh}, are shown in Fig. 3. Compounds **1a** without a substituent and **1b** with a methyl group at the 6-position did not suppress the oxidation. However, **1c** with a methoxy group *para* to the NH group suppressed the oxidation, as we previously observed.[4] Similarly, benzo[1,4]thiazine **2a** itself did not act as an antioxidant, but **2b** and **2c** with electron-donating groups proved good antioxidants. With a methoxy group *para* to the NH group, **2c** especially showed a marked increase in the t_{inh} value: 4 times that of **2a**. One of the most striking results of our study becomes apparent when the antioxidant activity for **3** is compared with **1** and **2**. 1,2,3,4-Tetrahydroquinoxaline **3a** without substituent acted as a potent antioxidant, as measured by t_{inh}. However, the introduction of methyl **(3b)** and methoxy **(3c)** groups to the phenyl ring have reactivities similar to or slightly less than that of **3a**. In general, the introduction of electron-donating groups to the phenol ring increases the antioxidant activity, whereas electron-attracting groups tend to decrease it.[12,13] That is, an electron-donating group causes an increase in the electron density of the OH oxygen. A peroxyl radical approaches the electron-rich oxygen and causes an electron transfer to the peroxyl oxygen atom from the electron-rich oxygen. The resulting basic peroxyl anion then abstracts the OH hydrogen as a proton. The generated phenoxyl radical then reacts with another peroxyl radical to form

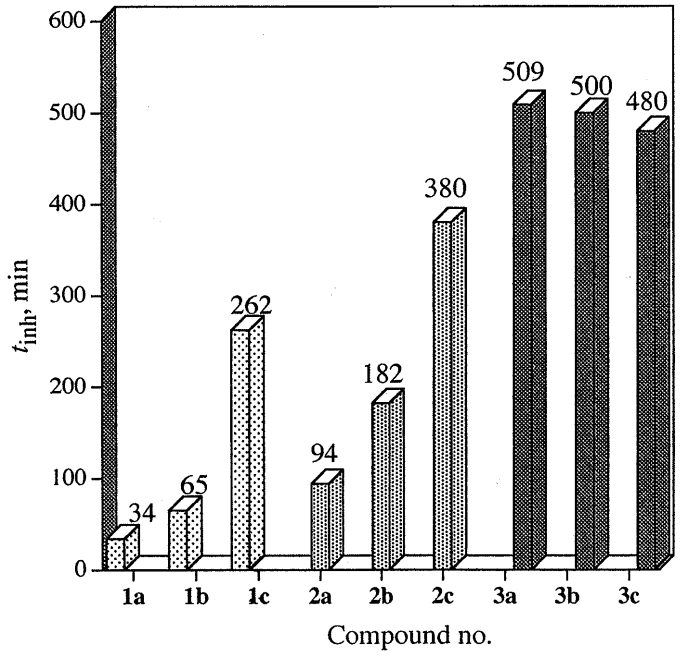


Fig.3 Oxidation inhibition by 1.0 mM antioxidants in tetralin induced by 10.0 mM AIBN at 61℃ under oxygen

peroxydienone. From these results, we can see that the antioxidant activity of 1,2,3,4-tetrahydroquinoxalines depends not only on the amino hydrogens themselves, but on another kind of hydrogen.

1,2,3,4-Tetrahydroquinoxalines with alkyl groups on the heterocyclic ring were also examined to clarify the effect of antioxidant activity. The t_{inh} values determined for various compounds **3d-3h** are shown in Table 1. The t_{inh} values of compounds **3d-3h** with an alkyl group or phenyl group to the 2 position are all longer than the value for the unsubstituted 1,2,3,4-tetrahydroqinoxaline **3a**, except for **3g** with a *t*-butyl group. In particular, the antioxidant activity, as measured by t_{inh}, for compounds **3h** with a phenyl group (760 min) was higher than that found for **3a** (509 min) and Nonflex (281 min). These results suggest

Table 1 Antioxidant activities, yields of oxidation products and bond dissociation energies of N-H and C-H bonds

Compd	t_{inh} [a]	yield; % [a, b]		BDE; kJ/mol			
No	min	quinoxaline	dimer	N(1)-H	N(4)-H	C(2)-H	C(3)-H
3a	509	18	39	353.9	353.9	322.2	322.2
3d	641	36	51	356.9	352.7	307.1	323.4
3e	698	36	40	361.5	353.5	306.3	323.0
3f	584	35	51	358.9	351.0	303.3	318.4
3g	464	11	55	356.9	351.0	306.3	324.7
3h	760	57	2	364.0	353.1	306.3	327.2
AW	281	-	-	-	-	-	-

a: Reaction conditions are the same as those in Fig. 3. b: yield after 200 min.

that the methylene group on the 2- and/or 3-positions of 2,3,4-tetrahydroquinoxalines donate hydrogens to peroxyl radicals.

Previous work on the antioxidant activities of 1,2,3,4-tetrahydroquinoxaline has suggested that tetrahydroquinoxaline scavenges a peroxyl radical to yield an intermediate radical, and then it reacts with another radical to yield an *ortho*-benzoquinone diimine-type product.[8] But no experimental evidence has confirmed that such an *ortho*-benzoquinone diimine is produced. To confirm the oxidation products of 1,2,3,4-tetrahydroquinoxaline, we carried out the following reaction. Compound **3a** [89.5 mM], AIBN [179.1 mM], and undecane [52.5 mM], as an internal standard, were dissolved in benzene, and the homogeneous mixture was stirred at 61℃ under oxygen. Both the consumption of **3a** and the formation of oxidation products were monitored by GLC at appropriate time intervals, as shown in Fig. 4.

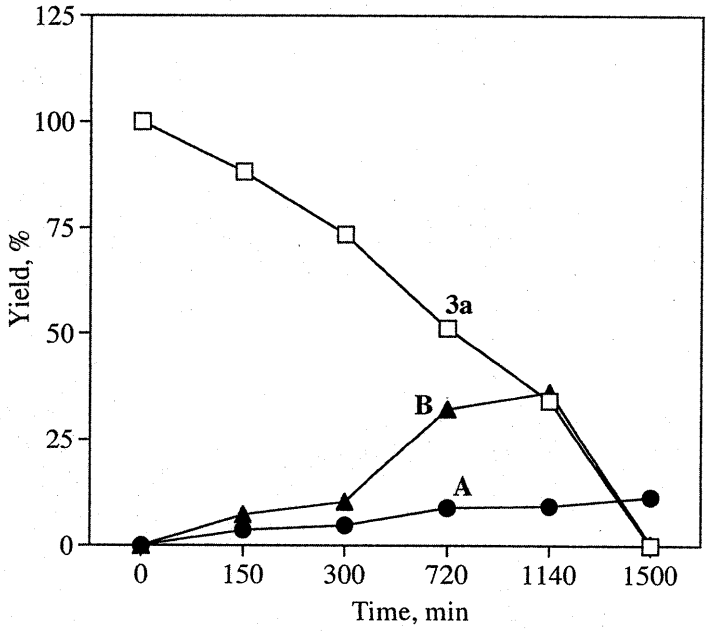


Fig.4 Relationship between consumption of **3a** and profile of oxidation products A and B during oxidation of 89.5 mM **3a** initiated by 179.1 mM AIBN in benzene at 61 ℃ under oxygen

As the substrate **3a** was consumed linearly with time, the oxidation products A and B appeared simultaneously. The oxidation product B gradually increased, and after reaching a maximum 36% yield, then decreased, indicating its high reactivity to peroxyl radical. On the other hand, the oxidation product A was produced very slowly. The structure of product A was determined by GC-MS spectroscopy, which gave *m/z* 130 as an M^+ ion, which is 4 less than the M^+ ion (134) of **3a**. The fragmentation pattern and the ^1H NMR agreed with an authentic sample of quinoxaline. From these results, we can see that the antioxidant activity of 1,2,3,4-tetrahydroquinoxalines depends not only on the two NH groups, but also on the two protons at the 2- and 3-positions. That is, 1,2,3,4-tetrahydroquinoxaline **3a** can trap a maximum of four peroxyl radicals per molecule.

On the other hand, the GC-MS of product **B** showed 262 as an M^+ ion, indicating a dimer of 1,2,3,4-tetrahydroquinoxaline. In the ^1H NMR of product B, signals at δ 3.49 (t, J=4.8 Hz, 2H) and δ 3.86 (t, J=4.8 Hz, 2H) suggest the existence of a -NCH_2-CH_2N- group. Other typical signals were also found at δ 8.68 (d, J=2.0 Hz, 1H) and δ 8.61 (d, J=2.0 Hz, 1H), indicating the presence of two imine protons (-N=CH-). The aromatic protons resonated at δ 6.61-6.66 (m, 2H), δ 6.82-6.85 (m, 1H), δ 7.01-7.10 (m, 1H), δ 7.54-7.55 (m, 1H), δ 7.77-7.79(m, 1H), and δ 7.81-7.93(m, 1H). In the ^{13}C NMR of product B, the -NCH_2-CH_2N- carbons resonated at δ 41.3 and 46.9. The aromatic and imine carbons appeared at δ 115.0-148.7 as 14 peaks. From these results, it can be assumed that the structure of product **B** is 6-(1,2,3,4-tetrahydroquinoxalin-1-yl)-quinoxaline. To estimate the reaction mechanism of the dimer products, we carried out the oxidation of quinoxaline in the presence of AIBN under similar conditions to those above. However, in this reaction no detectable amount of the dimer product was found, and the quinoxaline was recovered unchanged after 4 hr. From these results, the radical scavenging reaction by 1,2,3,4-tetrahydroquinoxaline **3a** in the oxidation of tetralin induced by AIBN could be deduced (see Fig. 5). In the case of paths a and b, **3a** can trap four and three peroxyl radicals per molecule, respectively.

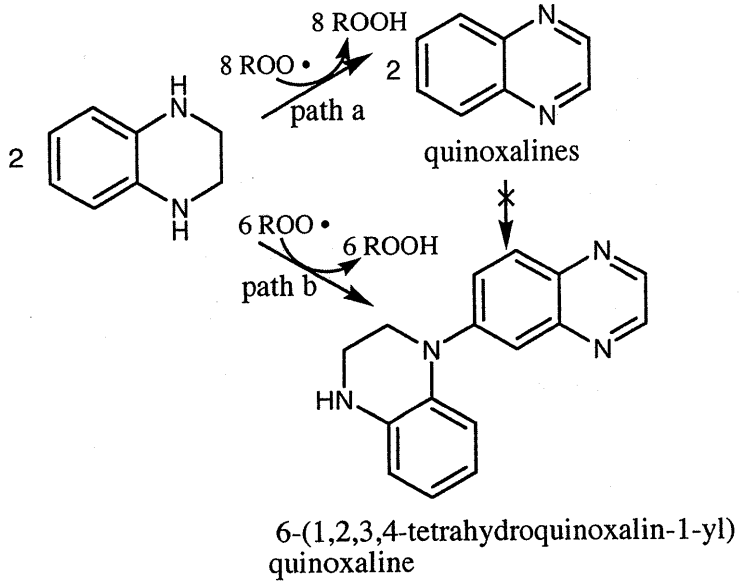


Fig.5 Radical scavenging reaction by 1,2,3,4-tetrahydroquinoxaline in the oxidation of tetralin induced by AIBN under oxygen

The oxidation of **3d-3h** was also carried out under similar conditions to those in Fig. 3. The corresponding quinoxaline and dimer product in each case was formed, as shown in Table 1. A comparison of the yield of quinoxaline and dimer products for **3a** and **3d-3f** reveals that the product rate of imines had increased in the order **3g<3a<3f, 3e, 3d<3h**. On the other hand, the product rate of dimers decreased in the order: **3g>3f>3d>3e>3a>3h**. These results suggest that decreasing the t_{inh} value tends to increase the yield of dimer product.

The vast majority of phenolic antioxidant (ArOH) can trap two peroxyl radicals, according to eqs.1 and 2[14,15]:

$$ROO\bullet + ArOH \rightarrow ROOH + ArO\bullet \quad (1)$$

$$ROO\bullet + ArO\bullet \rightarrow \text{nonradical product} \quad (2).$$

Effective phenolic antioxidants yield phenoxyl radicals that are relatively unreactive toward one another (eq. 3)[16,17] and toward molecular oxygen (eq. 4).[18] If reactions (3) and (4) occur during the induction period, phenols probably cause a decrease in the t_{inh} value. Since reaction (3) wastes an active phenoxyl

$$ArO\bullet + ArO\bullet \rightarrow \text{dimer product} \quad (3)$$

$$ArO\bullet + O_2 \rightarrow \text{radical product} \quad (4)$$

radical, which is used to trap a peroxyl radical, the radical product produced from reaction (4) is active and capable of initiating a chain oxidation. These lower the overall antioxidant activity.[19,20] The results and discussion given above suggest that the comparatively higher activity of compound **3h** may be attributed to the reduced yield of the dimer product, as compared to other 1,2,3,4-tetrahydroquinoxalines **3**.

Efficient phenolic antioxidants are known to terminate the peroxidation of free radical chains by donating a phenolic hydrogen atom, reaction (1). A high rate of reaction (1) is expected to directly correspond to a low O-H bond dissociation energy (BDE). Considerable effort has been devoted to the measurement of O-H BDE's for phenols.[21-23] Therefore, to confirm the oxidation mechanisms, we calculated the BDE value of the N-H and C-H bonds for 1,2,3,4-tetrahydroquinoxalines **3** (Table 1). The N-H BDE for **3a** without a substituent at the 2-position was estimated to be 31.7 kJ/mol stronger than the C-H bond. The question consequently arises: which hydrogens can trap a peroxyl radical first?

To address this question, we calculated the BDE of piperazine, which is structurally related to **3**. In spite of a low C-H BDE (C-H=307.1, N-H=361.1 kJ/mol), piperazine did not act as an antioxidant. Based on these results, we suggest that **3** suppresses the oxidation by the following two mechanisms, as shown in Fig. 6. At first, peroxyl radicals abstract the N-H hydrogen from **3**. Then, the resulting 1,2,3,4-tetrahydroquinoxalinyl radical (**C**) scavenges a peroxyl radical, forming (**D**). Furthermore, peroxyl radicals abstract the C(2)-H and N(1)-H hydrogens from **D** to form the quinoxaline.

The results seen in Table 1 suggest that decreasing the t_{inh} value tends to increase the yield of the dimer product. This is probably because the intermediate radical **C** can also be dimerized. That is, the radical in the structure **E**[24] is distributed on the heterocyclic ring (e.g. **F**) and is also able to exhibit a resonance with the phenyl group, such as structure **G**. Radical **G** can undergo a C-N coupling reaction with radical **C** to form the dimer product. However, the phenyl group on the 2-position in radicals **E**～**G** contributes additional stability to the intermediate radical by electron delocalization with a 2-phenyl ring (radical **H**). This stabilized radical **H** cannot undergo a C-N coupling reaction to form a dimer product. Next, we calculated the BDE of the C(2)-H and N(1)-H bonds for 1,2-dihydroquinoxalines **D** (see Fig 6) to clarify the effect of the phenyl group on the 2-position on the stabilization of the radical **H**. The BDE values for **D** are listed in Table 2. In fact, the C(2)-H BDE of **3h** with the phenyl group is 4～15 kJ/mol weaker than that of other 1,2-dihydroquinoxalines.

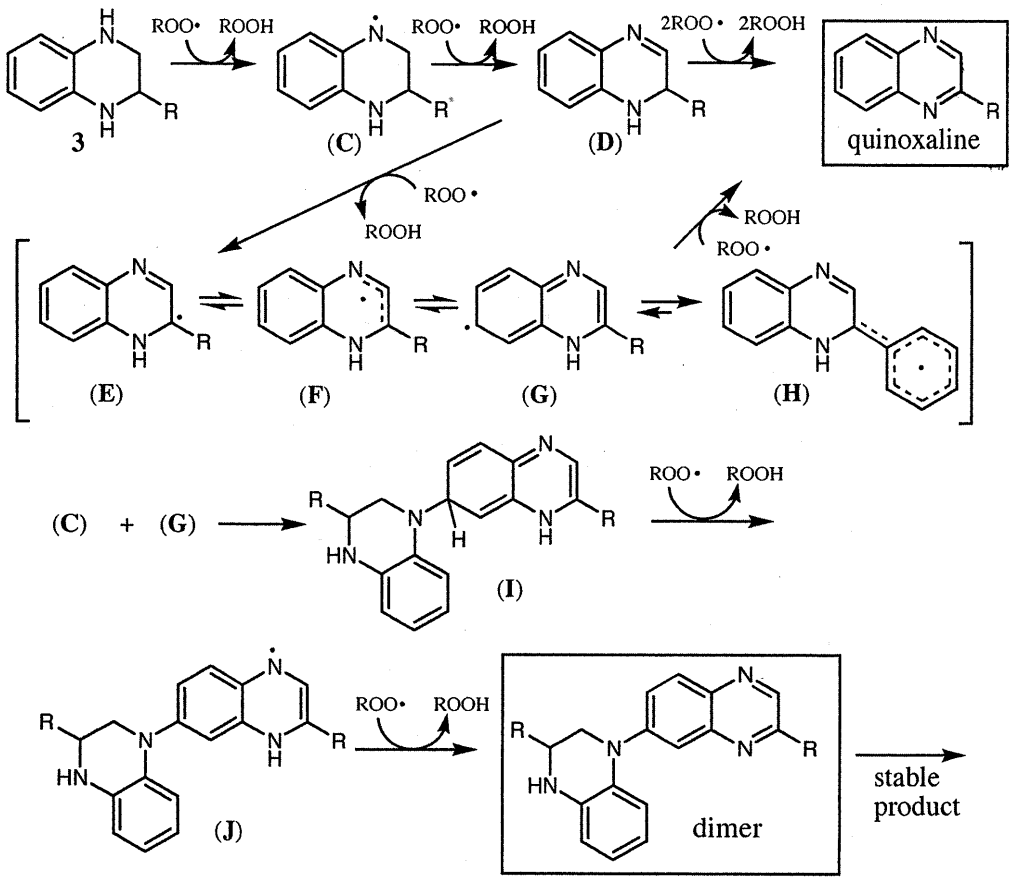
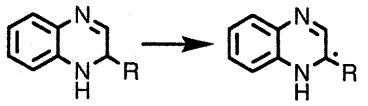


Fig.6 Proposed chain-breaking mechanisms for 1,2,3,4-tetrahydroquinoxalines 3

Table 2 Calculated bond dissociation energy, D(N(1)-H) and D(C(2)-H), for 1,2-dihydroquinoxalines D



R	N(1)-H	C(2)-H
	kJ/mol	
H	359.4	294.1
Me	370.7	283.7
Et	371.9	285.7
i-Pr	370.3	285.3
t-Bu	371.9	286.6
Ph	375.3	279.1

In conclusion, hydrogen-atom abstraction from 1,2,3,4-tetrahydroquinoxalines **3** by a peroxyl radical yields quinoxalines and dimer products. Looking at the relationship between the yield of oxidation products and the t_{inh} values, it was found that the phenyl group on the 2-position must play an important role in the high antioxidant activity of **3**. Although an antioxidant of amine derivatives during and after induction period turns in to a deep-red solution, it is noteworthy that the color of 1,2,3,4-tetrahydroquinoxalines **3** after induction period was a pale yellowish solution. Thus, compound **3h** may be an effective antioxidant for preventing the oxidation of plastics, oils and rubber products.

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