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Mechanism of Inhibition of Lipid Peroxidation by γ -Terpinene, an Unusual and Potentially Useful Hydrocarbon Antioxidant

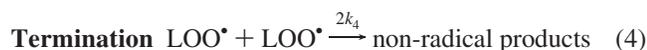
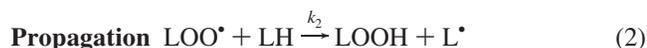
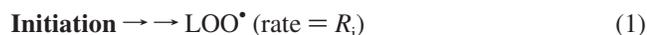
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γ -Terpinene (TH), a monoterpene hydrocarbon present in essential oils, retards the peroxidation of linoleic acid (LH). The peroxidation of TH has been shown to yield *p*-cymene as the only organic product in a chain reaction in which the chain carrier is the hydroperoxyl radical, HOO \cdot . The peroxidation of LH is well-known to be a chain reaction in which the chains are carried by linoleylperoxy radicals, LOO \cdot , and the products are linoleyl hydroperoxides. The retardation of LH peroxidation by TH has been found to be due to rapid chain termination via a very fast cross-reaction between HOO \cdot and LOO \cdot radicals. This antioxidant mechanism is completely different from the mechanism of antioxidant action of vitamin E. Since vitamin E becomes a prooxidant at high concentrations, the addition of essential oils containing TH to edible lipids may provide an alternative or supplementary strategy for obtaining large increases in their oxidative stability and shelf life, something that cannot be achieved by simply adding more and more vitamin E.

KEYWORDS: Antioxidant; hydroperoxyl radical; kinetics; peroxidation; terpinene

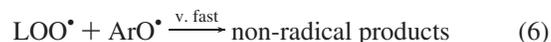
Essential oils derived from aromatic and medicinal plants have been known for thousands of years to have biological activities (1, 2). Much more recently, it has been demonstrated that essential oils have antibacterial, antimycotic, and, in a number of cases, antioxidant activities (3–5), which opens the possibility of using these oils as preservatives for food and cosmetics—at least where “their use is not in contrast with their aroma” (6). Essential oils are complex mixtures containing mono- and sesquiterpenes, oxygenated terpenes, *phenols*, and other compounds (7, 8). Their antioxidant activity is not surprising in view of the presence of phenols, ArOH, since it is well-known that almost all phenols can function as antioxidants of lipid peroxidation because they trap the chain-carrying lipid peroxy radicals, LOO \cdot (9). The lipid, LH, peroxidation process is normally represented by



In the presence of a phenol, the rate of peroxidation will

generally be greatly reduced because the chain length is decreased by the reactions:

Termination by ArOH



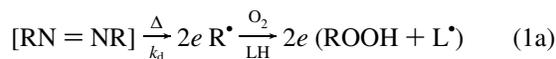
For good phenolic antioxidants, such as the tocopherols (9), the rate constant for peroxy radical trapping, k_5 , is some 4–5 orders of magnitude greater than the rate constant for the rate-controlling propagation step, k_2 , which normally involves hydrogen atom abstraction from a polyunsaturated fatty acid (PUFA) moiety. Thus, low concentrations of good phenolic antioxidants can compete very effectively with the lipid for the available peroxy radicals even when they are present at very much lower concentrations than PUFAs.

The foregoing “simple” explanation for the observed antioxidant activities of essential oils in terms of their content of phenols represents, however, only a part of the picture. Recently, Ruberto and Baratta (6) tested about 100 pure compounds present in essential oils for their antioxidant activity. Two different model systems were employed: one involved an egg yolk homogenate as the oxidizable substrate and the other involved linoleic acid in SDS micelles. In both systems, peroxidation was initiated by thermal decomposition of 2,2'-azobis(2-amidinopropane) to maintain a constant rate of chain initiation (10), R_i (eqs 1 and 1a)

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$$R_i = 2ek_d [\text{RN} = \text{NR}] \quad (7)$$

where e is the efficiency of cage escape of the initial geminate pair of radicals. Very surprisingly, three monoterpene hydrocarbons exhibited significant antioxidant activities, with γ -terpinene, TH (which is present in essential oils in variable amounts up to 50% (8)), showing the highest activity. The antioxidant indices (as a percentage of the nonperoxidized control) for the three active monoterpenes, γ -terpinene, α -terpinene, and terpinolene, at 500 ppm in the egg yolk system in fact were 76, 57, and 56% (vs 89% for α -tocopherol), respectively, and at 10^{-3} M in the linoleic acid system were 79, 73, and 22% (vs 92% for α -tocopherol), respectively (6). Later, Elstner and co-workers demonstrated antioxidant activities for γ -terpinene and terpinolene in the copper-induced oxidation of human low-density lipoprotein (11).

These results are exciting for two reasons. First, γ -terpinene is readily peroxidizable, *Vide infra*, and only very rarely have readily peroxidizable hydrocarbons such as triphenylmethane (12), β -carotene (13), and tetralin (14) been shown to have antioxidant activities. Second, although low concentrations of α -tocopherol provide good short-term, ambient temperature, protection to edible oils against peroxidation, long-term protection at elevated temperatures is poor. Moreover, increasing the α -tocopherol concentration in the hope of improving protection is counterproductive because this "antioxidant" then becomes a "prooxidant" (15). For example (15d), the self-initiated peroxidation of neat methyl linolenate at 40 °C for 100 h produced conjugated dienes (a sign of hydroperoxide formation) in yields ($\mu\text{mol/g}$) of 665, 42, 74, and 469 at 0.0, 0.05, 0.5, and 5.0% α -tocopherol, respectively, while, even more surprisingly, methyl linoleate gave yields of 364 and 432 $\mu\text{mol/g}$ at 0.0 and 5.0% α -tocopherol, respectively. The chemistry underlying this prooxidant behavior is well-understood (16), and this process is known today as tocopherol mediated peroxidation (TMP) (17). Since large increases in oxidative stability and shelf life for edible oils cannot be achieved by adding more vitamin E, alternative and/or supplementary strategies for achieving this goal are well worth pursuing. With this thought in mind, we undertook the present investigations into the mechanism of peroxidation of TH and of its antioxidant activity toward linoleic acid, LH.

MATERIALS AND METHODS

Materials and Instrumentation. γ -Terpinene (>99%) was purchased from Fluka and used as received; 2,2'-azobis(isobutyronitrile), AIBN (>98%), from Merck, was recrystallized from methanol and stored at -20 °C; linoleic acid (>99%) was obtained from Sigma and passed over silica gel in a glass pipet before use. Cyclohexane and acetonitrile were purchased from Merck and were of HPLC grade. The kinetics were monitored on a Perkin-Elmer Lambda 25 UV/VIS double ray spectrometer; the NMR spectra were recorded on a Bruker AC-250 spectrometer operating at 250 (^1H) and 62.9 (^{13}C) MHz and the GC-MS analyses were done on a Hewlett-Packard 5890 interfaced to a Hewlett-Packard 5971A Mass Selective detector (DB-5 capillary column, 30 m \times 0.25 mm, film thickness 0.25 μm).

Peroxidation of γ -Terpinene. Solutions of γ -terpinene (final concentration 2–140 mM) and AIBN (final concentration 2–50 mM in acetonitrile and 1–5 mM in cyclohexane) were prepared in the solvent in use, mixed 1:1 (v/v) in a UV-cuvette (optical path, either 1.0 or 0.5 cm) and saturated with air or oxygen at 1 atm. After thermal equilibration in the cell compartment at 50 °C (5 min), the absorbance

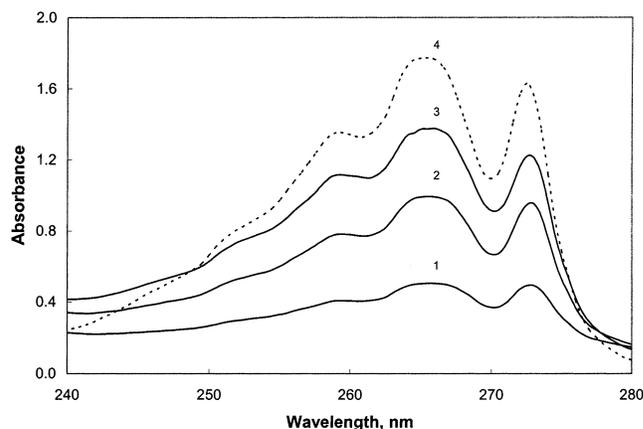


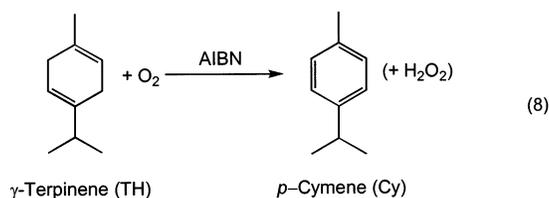
Figure 1. Growth in UV absorbance during peroxidation of 12.3 mM TH in acetonitrile initiated with 29.8 mM AIBN at 50 °C. Key: Spectral traces 1, 2, and 3 were recorded after 10, 35, and 48 min. Trace 4 is the spectrum of authentic p -cymene (4.12 mM).

at, or near, the maximum in the UV spectrum of p -cymene was monitored over time. Excellent straight lines ($R^2 = 0.97$ – 0.99) of absorbance vs time were usually obtained whose slopes (divided by ϵ_l and, in the case of cuvettes of 0.5 cm, multiplied by 2) gave the rate of reaction, $d[\text{Cy}]/dt$ in M/s. The reaction orders for AIBN and γ -terpinene were obtained by changing the concentration of one species while keeping the other constant. The slopes of the plots $(d[\text{Cy}]/dt)$ vs $\log([\text{TH}])$ or $[\text{AIBN}]$ gave the desired reaction orders.

Peroxidation of Linoleic Acid and Inhibition Effect of γ -Terpinene or 1,4-Cyclohexadiene. Solutions of linoleic acid (final concentration 10–50 mM) and AIBN (final concentration 2–5 mM) were prepared in the solvent in use and mixed 1:1 (v/v) in a UV-cuvette. Scalar volumes (10–80 μL) of a stock solution (20–40 mM) of TH or CHD were then added along with a complementary volume of up to 100 μL of solvent to keep the final volume of the solution constant. After waiting (5 min) for thermal equilibration (50 °C) in the cell-compartment, the rate of peroxidation of linoleic acid was monitored at 234 nm. The slope of the abs/time plot divided by the extinction coefficient at 234 nm (see text) of linoleoyl hydroperoxides, LOOH, gave the rate of reaction, $d[\text{LOOH}]/dt$ in M/s.

RESULTS

Peroxidation of γ -Terpinene. The kinetics of this reaction was studied at 50 °C in acetonitrile and cyclohexane. The reaction was initiated by the thermal decomposition of 2,2'-azobis(isobutyronitrile), AIBN (reaction 1a, $\text{R} \cdot = (\text{CH}_3)_2\text{C} \cdot \text{CN}$). Peroxidation was monitored by changes in the UV absorption spectrum. Overlapping bands at ca. 259, 265, and 272 nm grow in and since these bands correspond to those observed with an authentic sample of p -cymene, Cy (see Figure 1), it is obvious that Cy is the major organic product (p -cymene is also produced in the photooxidation of α -terpinene (18)):



In fact, Cy would appear to be the sole organic product since no terpenyl hydroperoxides nor any other oxygenated organics were formed in significant amounts as judged by GC-MS and ^1H NMR in CD_3CN . Furthermore, the UV absorption spectrum rules out any significant yield of conjugated terpenyl

Table 1. Determination of the Kinetics of the AIBN Initiated Peroxidation of TH in Acetonitrile at 50 °C

[TH] (mM)	[AIBN] range (mM)	order in AIBN ^a	[AIBN] (mM)	[TH] range (mM)	order in TH ^a
8.65	2.12–48.2	0.49	3.80	16.1–64.5	1.03
64.5	1.11–14.3	0.63	17.3	27.0–136.4	1.00
121.5	4.83–48.3	0.45	29.5	2.5–49.5	0.93
			30.96	3.0–121.5	0.84

^a Reaction orders were determined by varying the concentration of one reactant while keeping the other reactant concentration constant. At least five different concentrations of the reactant being varied were employed and all plots of R_{Cy} vs [AIBN] and vs [TH] gave excellent straight lines, $R^2 \geq 0.97$.

hydroperoxides (analogous to the hydroperoxides formed during peroxidation of linoleic acid) because such hydroperoxides should, according to Woodward's rules (19), have $\lambda_{max} \approx 269$ nm with extinction coefficients ≈ 5000 – 8000 $M^{-1} cm^{-1}$. Since the ϵ_{265} for *p*-cymene is only 418 $M^{-1} cm^{-1}$ (see **Figure 1**) even traces of conjugated hydroperoxides would be readily detected.

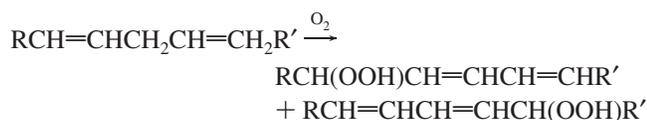
The kinetics of TH peroxidation in acetonitrile and cyclohexane at 50 °C were determined spectrophotometrically by following the increase with time in the absorbances at 272 nm ($\epsilon = 390$ $M^{-1} cm^{-1}$ in acetonitrile and 394 $M^{-1} cm^{-1}$ in cyclohexane), 270 nm ($\epsilon = 257$ $M^{-1} cm^{-1}$ in acetonitrile and 234 $M^{-1} cm^{-1}$ in cyclohexane), and/or 265 nm ($\epsilon = 418$ $M^{-1} cm^{-1}$ in CH_3CN and 408 $M^{-1} cm^{-1}$ in cyclohexane, all at 50 °C) under 760 Torr air or oxygen. The range of TH concentrations was ca. 2.5–140 mM and AIBN concentrations was ca. 2–50 mM in acetonitrile (1–5 mM in cyclohexane). No differences in the rates of Cy formation were found between the air- and oxygen-saturated systems under any of these conditions. The kinetic results are summarized in **Table 1**. The experimental rate of formation of Cy, R_{Cy} , in acetonitrile can be described by

$$R_{Cy}/M s^{-1} = (4.4 \pm 0.3) \times 10^{-4} \times [AIBN]^{0.52 \pm 0.09} \times [TH]^{0.95 \pm 0.08} \quad (9)$$

A similar rate law was obeyed for TH peroxidation in cyclohexane at 50 °C, viz.,

$$R_{Cy}/M s^{-1} = (9.1 \pm 0.9) \times 10^{-5} [AIBN]^{0.50 \pm 0.08} [TH]^{0.95 \pm 0.05} \quad (10)$$

Inhibition of Peroxidation of Linoleic Acid by γ -Terpinene. The AIBN initiated peroxidation of LH was monitored at 50 °C by following the grow-in of the absorbance due to diene conjugation at 234 nm in cyclohexane ($\epsilon_{234} = 25$ 500 $M^{-1} cm^{-1}$) and acetonitrile ($\epsilon_{234} = 29$ 100 $M^{-1} cm^{-1}$) as described previously (20), eq 11.



linoleic acid, LH: $R = CH_3(CH_2)_4$, $R' = HO_2C(CH_2)_7$ (11)

This technique is fairly sensitive because of the large 234 nm extinction coefficients of the conjugated diene hydroperoxides, a wavelength where neither TH nor Cy absorb significantly ($\epsilon_{234} = 30$ and 41 $M^{-1} cm^{-1}$, respectively, in acetonitrile

Table 2. Rates of Peroxidation of Linoleic Acid (LH) in the Absence and Presence of γ -Terpinene (TH) at 50 °C in Cyclohexane and Acetonitrile Initiated with AIBN and Measured Spectrophotometrically at 234 nm

solvent	cyclohexane		acetonitrile	
	[LH]/mM	[AIBN]/mM	[TH]/ μ M	d[LOOH]/dt (nM s ⁻¹) ^{a,c}
	30.3	0.882		20.4
				1.141
	[TH]/ μ M	d[LOOH]/dt (nM s ⁻¹) ^{a,b}	[TH]/ μ M	d[LOOH]/dt (nM s ⁻¹) ^{a,c}
	0	30	0	36
	59.5	26	51.5	25
	119	23	103	17
	237	20	206	13
	475	16	412	10
	712	14	618	6
	950	12	824	5
	1420	10.5		

^a Reproducibility was better than or equal to $\pm 20\%$. ^b From 234 nm absorbance vs time plots using $\epsilon_{234} = 25$ 500 $M^{-1} cm^{-1}$. ^c From 234 nm absorbance vs time plots using $\epsilon_{234} = 29$ 100 $M^{-1} cm^{-1}$.

Table 3. Rates of Peroxidation of Linoleic Acid (LH) in the Absence and Presence of 1,4-Cyclohexadiene (CHD) at 50 °C in Cyclohexane and Acetonitrile Initiated with AIBN and Measured Spectrophotometrically at 234 nm

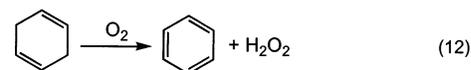
solvent	cyclohexane		acetonitrile	
	[LH]/mM	[AIBN]/mM	[CHD]/ μ M	d[LOOH]/dt (nM s ⁻¹) ^{a,c}
	26.8	2.74		29.9
				2.22
	[CHD]/ μ M	d[LOOH]/dt (nM s ⁻¹) ^{a,b}	[CHD]/ μ M	d[LOOH]/dt (nM s ⁻¹) ^{a,c}
	0	41	0	99
	99.2	39	97	75
	198	38	194	64
	595	33	388	47
	992	28	582	37
	1570	23	776	30
			970	26

^a Reproducibility was better than or equal to $\pm 20\%$. ^b From 234 nm absorbance vs time plots using $\epsilon_{234} = 25$ 500 $M^{-1} cm^{-1}$. ^c From 234 nm absorbance vs time plots using $\epsilon_{234} = 29$ 100 $M^{-1} cm^{-1}$.

at 50 °C). Plots of the absorbance at 234 nm against time gave excellent straight lines both in the absence and presence of TH. The slopes of these plots were converted to rates of LH peroxidation using the ϵ_{234} value appropriate to the solvent (cyclohexane or acetonitrile) in which the reaction was carried out. Similar experiments were performed using 1,4-cyclohexadiene (CHD) in place of TH. Some of these results are summarized in **Tables 2** and **3** and shown graphically in **Figures 2** and **3** as plots of the ratio, $R_{LH}^{TH \text{ or } CHD}/R_{LH}^0$, of the peroxidation rates in the presence of TH or CHD to the rate in the absence of these compounds.

DISCUSSION

The peroxidation of γ -terpinene (TH) to *p*-cymene (Cy) as the sole organic product (reaction 8) resembles the peroxidation of CHD, which yields benzene as the sole organic product (21) and hydrogen peroxide (21b) (reaction 12).



The chain, carrying peroxy radical involved in reaction 12, has been unequivocally identified as the hydroperoxy radical (21b).

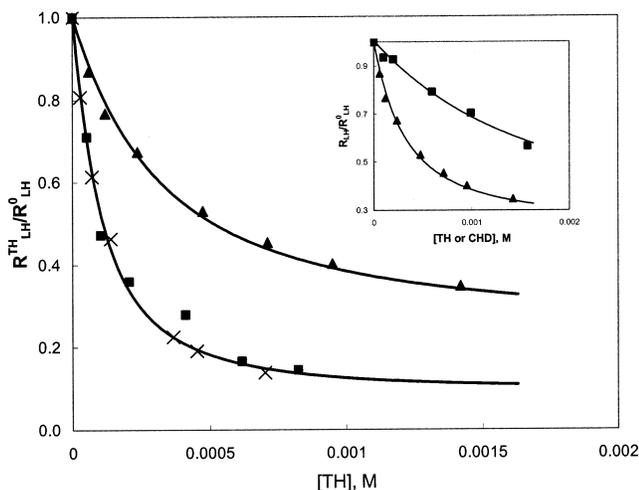
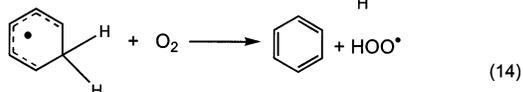
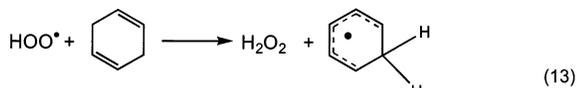
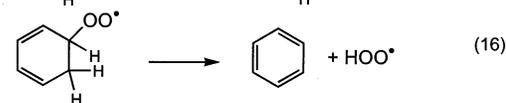
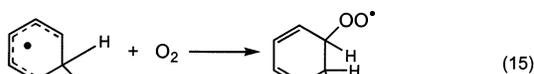


Figure 2. Ratio of the rate of peroxidation of LH in the presence of TH, R_{LH}^{TH} , to the rate in the absence of TH, R_{LH}^0 , as a function of TH concentration at 50 °C. Key: \blacktriangle in cyclohexane, $[LH] = 30.3$ mM, $[AIBN] = 0.882$ mM; \blacksquare in acetonitrile, $[LH] = 20.4$ mM, $[AIBN] = 1.41$ mM; \times in acetonitrile, $[LH] = 14.0$ mM, $[AIBN] = 1.02$ mM. The solid lines were calculated using the mechanism and kinetics reported in the text, which yielded the following values of k_{32} and k_{33} (in $M^{-1} s^{-1}$ units): ca. 2200 and 350, respectively, both in acetonitrile and cyclohexane. Only the solid line fitted to the set of data (\times) is represented in acetonitrile since the fit to the other set (\blacksquare) is virtually identical. Inset: Comparison of the antioxidant activities of TH (\blacktriangle) ($[LH] = 30.3$ mM; $[AIBN] = 0.9$ mM) and CHD (\blacksquare) ($[LH] = 30.3$ mM; $[AIBN] = 0.9$ mM) (as ratio $R_{LH}^{CHD \text{ or TH}} / R_{LH}^0$) in cyclohexane at 50 °C toward linoleic acid.

Reactions 13 and 14 constitute the two steps of propagation.



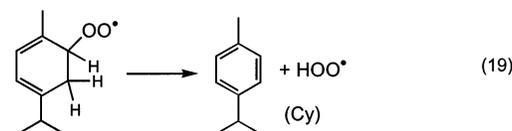
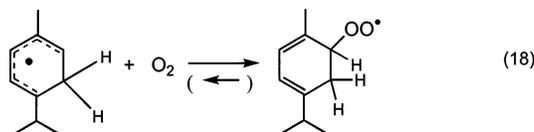
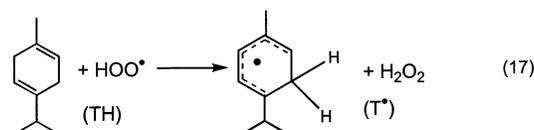
It was initially proposed that reaction 14 followed an addition–elimination pathway (21b), reaction 15, which is essentially diffusion controlled, $k_{15} \sim 10^9 M^{-1} s^{-1}$ (22), and reaction 16.



Later, a direct H-atom abstraction from the cyclohexadienyl radical by O_2 was suggested (21c). However, the two-step mechanism for CHD oxidation (reactions 15 + 16) and, by analogy, for TH oxidation, is supported by three independent lines of evidence: (i) The peroxidation of 1,4-dihydronaphthalene (DHN) at low $[DHN]$ yields naphthalene and H_2O_2 , but at high $[DHN]$ the product is a DHN hydroperoxide indicating that the initial adduct peroxy radical has been trapped by DHN in a “normal” propagation step (21b). With 9,10-dihydroanthracene (DHA) even at low concentrations, the product is a DHA hydroperoxide (21b). (ii) During the pulse radiolysis of CHD in water the adduct radical, $c\text{-C}_6\text{H}_7\text{OO}^{\bullet}$ has been detected (22b) and, during the pulse radiolysis of benzene in water, the

$c\text{-C}_6\text{H}_6(\text{OH})\text{OO}^{\bullet}$ radical (23). (iii) The direct H-atom abstraction mechanism was based on the hypothesis that reaction 15 was reversible, which is certainly true for other dienyloxy radicals (24). However, the equilibrium was suggested to lie strongly to the left because the O–C bond dissociation enthalpy (BDE) in $c\text{-C}_6\text{H}_7\text{OO}^{\bullet}$ was estimated to be only 5 ± 2 kcal/mol (21c). However, this O–C BDE is currently estimated to be 12 kcal/mol (25), which implies that the β -scission of $c\text{-C}_6\text{H}_7\text{OO}^{\bullet}$ (reaction –15) is slow and, hence, that the equilibrium of reaction 15 lies to the right except at very low O_2 concentrations and elevated temperatures.

The kinetics observed for the peroxidation of TH at the low concentrations employed (eqs 9 and 10) are the same as those reported for CHD at similarly low concentrations (21b,c). Since both reactions yield a single aromatic product (viz., *p*-cymene and benzene), it is safe to assume that the two peroxidation chains involve similar steps. Oxygen addition to cyclohexadienyl radicals will occur at close to the diffusion-controlled limit whether a nonconjugated or conjugated dienyloxy radical is formed. However, loss of oxygen from the nonconjugated dienyloxy radical will be several orders of magnitude faster than from the conjugated dienyloxy radicals (24), and the former peroxy radical will therefore play little or no role in the overall reaction. Hydrogen atom abstraction from both ring methylene groups will occur and oxygen may add to either end of the resulting pentadienyl radicals, but, for simplicity, only one of these possibilities is shown below.



In water, $k_{16} \geq 8 \times 10^5 s^{-1}$ (22b) and an equally high rate constant would be expected for reaction 19. Such rapid elimination of $HO\dot{O}^{\bullet}$ accounts for the absence of oxygenated organics from CHD and TH under the peroxidation conditions employed.

The AIBN initiated peroxidation of TH involves the initiation step 1a ($R = (\text{CH}_3)_2\text{CCN}$) and reactions 17–19 with chain termination by reaction 20.



This reaction sequence yields the following rate law for Cy formation:

$$R_{\text{Cy}} = R_i^{1/2} k_{17} [\text{TH}] / (2k_{20})^{1/2} \quad (21)$$

which is fully consistent with the observed kinetics (eqs 9 and 10). It should be noted that R_{Cy} is not dependent on the oxygen partial pressure (range ca. 150–760 Torr). This indicates that under the present experimental conditions: (i) There is no appreciable *direct* reaction between molecular oxygen and TH

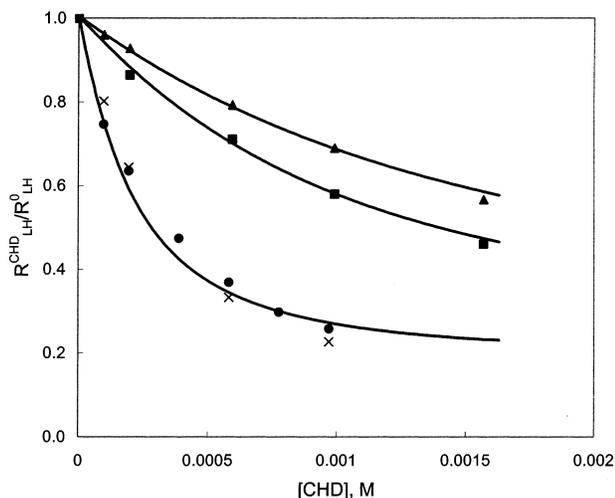
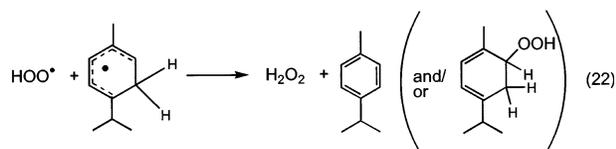


Figure 3. Ratio of the rate of peroxidation of LH in the presence of CHD, R_{LH}^{CHD} , to the rate in the absence of CHD, R_{LH}^0 , as a function of CHD concentration at 50 °C. Key: \blacktriangle in cyclohexane, [LH] = 26.8 mM, [AIBN] = 2.74 mM; \blacksquare in cyclohexane, [LH] = 13.4 mM, [AIBN] = 2.74 mM; \times in acetonitrile, [LH] = 29.9 mM, [AIBN] = 2.22 mM; \bullet in acetonitrile, [LH] = 15.3 mM, [AIBN] = 2.67 mM. The solid lines were calculated using the mechanism and kinetics reported in the text which yielded for k_{34} ca. $1200 \text{ M}^{-1} \text{ s}^{-1}$ and as before (Figure 2) $k_{33} = 350 \text{ M}^{-1} \text{ s}^{-1}$ both in cyclohexane and acetonitrile. Only the solid line fitted to the set of data (\bullet) is represented in acetonitrile since the fit to the other set (\times) is virtually identical.

(oxygen can directly initiate CHD peroxidation at 50 °C at relatively high CHD concentrations (ca. 1.0–10 M) (21c)). (ii) Chain termination occurs solely by reaction 20.

Sole termination via reaction 20 indicates that β -scission of γ -terpinenylperoxyl radicals, reaction -18, is not important under our conditions. That is, were T^* radicals present in solution in significant concentrations, chain termination would occur by the cross-reaction 22 because this reaction will be diffusion-controlled and hence considerably faster than reaction 20 (*Vide infra*).



Moreover, termination by reaction 22 would give a kinetic rate law dependent upon $[\text{O}_2]^{1/2}$ and $[\text{TH}]^{1/2}$, which is inconsistent with experiment (eqs 9 and 10).

For AIBN, $2ek_d$ (see eq 7) at 50 °C is equal to $2.0 \times 10^{-6} \text{ s}^{-1}$ in acetonitrile and $1.36 \times 10^{-6} \text{ s}^{-1}$ in cyclohexane (20). The oxidizability of TH, $k_{17}/(2k_{20})^{1/2}$, can therefore be calculated (via eqs 9, 10, and 21) to be $4.4 \times 10^{-4}/(2.0 \times 10^{-6})^{1/2} = 0.31 \text{ M}^{-1/2} \text{ s}^{-1/2}$ in acetonitrile and $9.1 \times 10^{-5}/(1.36 \times 10^{-6})^{1/2} = 0.078 \text{ M}^{-1/2} \text{ s}^{-1/2}$ in cyclohexane. Since k_{17} is expected to be about the same in acetonitrile and cyclohexane (21b), the ratio $(0.31/0.078)^2 = 15.8$ should equal the increase in $2k_{20}$ on passing from acetonitrile to cyclohexane. In a saturated hydrocarbon solvent (*n*-decane), $2k_{20}$ is ca. $1.3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ at 30 °C (21b) and since this is close to the diffusion controlled limit it will probably be about the same at 50 °C. The value of $2k_{20}$ in acetonitrile at 50 °C can therefore be estimated to be ca. $1.3 \times 10^9/15.8 = 8.2 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ from which k_{17} can be calculated to be $\sim 2800 \text{ M}^{-1} \text{ s}^{-1}$ at 50 °C in both solvents.

In the case of CHD, the value in acetonitrile and cyclohexane of k_{13} at 50 °C can be estimated to be ca. $890 \text{ M}^{-1} \text{ s}^{-1}$ from the values at 30 °C (21b) in acetonitrile and *n*-decane and the Arrhenius pre-exponential factor for H-atom abstraction, $A \sim 10^{8.5} \text{ M}^{-1} \text{ s}^{-1}$.

Inhibition of Peroxidation of Linoleic Acid by γ -Terpinene. There are two well-recognized mechanisms by which certain readily peroxidizable hydrocarbons, AH (12a,b, 13, 14a) (and their hydroperoxides, AOOH (12c, 14b)) can function as antioxidants. Hydrocarbons in Class 1 react rapidly with the substrate's (SH) chain-carrying peroxy radicals (SOO^\bullet) and form carbon-centered radicals (A^\bullet) which are strongly stabilized by resonance. As a consequence, the reactions of A^\bullet with oxygen are reversible and, *even under ambient conditions*, the equilibrium favors $\text{A}^\bullet + \text{O}_2$ rather than AOO^\bullet . The involvement of this equilibrium is evident from the increase in antioxidant effectiveness of AH (and AOOH) at low oxygen partial pressures and at elevated temperatures. Typical Class 1 AH antioxidants are triphenylmethane (12a,b) and β -carotene (13). Their mechanism of action is shown in reactions 23 to 25, and for AOOH, reaction 26 followed by reactions -24 and 25.



It will be obvious that Class 1 hydrocarbon antioxidants effective at low concentrations relative to SH must be highly reactive toward peroxy radicals, i.e., $k_{23} \gg k_2$. It will also be obvious that the kinetics of Class 1 AH-retarded peroxidations of SH will be dependent on the oxygen partial pressure, reaction 24.

The retardation of SH peroxidation by Class 2 hydrocarbon antioxidants also requires $k_{23} \gg k_2$, but it is not dependent on the oxygen partial pressure. Class 2 AHs decrease the steady-state concentration of the chain-carrying peroxy radicals (thereby reducing the peroxidation rate) because the rate constant for the cross-reaction between AOO^\bullet and SOO^\bullet is much greater than the rate constant for the bimolecular self-reaction of two SOO^\bullet radicals, i.e., $k_{27} \gg k_{28}$.



In practice this has meant that Class 2 AHs yield secondary (or primary) alkylperoxy radicals and they only exert significant antioxidant effects on SH substrates which yield tertiary S^\bullet radicals and hence tertiary alkylperoxy radicals. The classic (and best) example of this phenomenon is the retardation of cumene peroxidation by tetralin (14a); another example is the inhibition of cumene peroxidation by tertiary amines (26). The explanation for these restrictions on the nature of Class 2 AHs and the substrates for which they can be effective retarders lies in the rate constants for the bimolecular self-reactions of alkylperoxy radicals, $2k_{28}$. Typical values of $2k_{28}/\text{M}^{-1} \text{ s}^{-1}$ are ca. 10^3 – 10^4 for tertiary alkylperoxy radicals, ca. 10^7 for secondary, and ca. 10^8 for primary alkylperoxy radicals (27), and the mechanistic reasons for this range of $2k_{28}$ values are well understood (14a, 27). Rate constants for the cross-reactions between secondary and tertiary alkylperoxy radicals are, on mechanistic grounds (14a, 27), expected

to be about half the value for the self-reaction of the secondary peroxy radical involved.

Since TH retards the peroxidation of linoleic acid with no oxygen pressure dependence, it cannot be a Class 1 hydrocarbon antioxidant and must therefore belong to Class 2. This means that the “cross” hydroperoxyl/peroxy termination process (reaction 29)

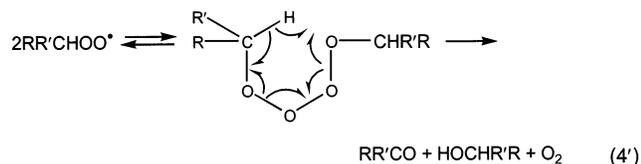


must be much faster than the bimolecular self-reaction of (secondary) linoleylperoxy radicals for which $2k_4 = 8.8 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 30 °C (27a) and ca. $3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ at 50 °C. (At 30 °C $k_2 \approx 60 \text{ M}^{-1} \text{ s}^{-1}$ (27a) and the Arrhenius preexponential factor, A , assumed to be ca. $10^{8.5} \text{ M}^{-1} \text{ s}^{-1}$ per reactive H-atom, yield $k_2 \approx 163 \text{ M}^{-1} \text{ s}^{-1}$ at 50 °C. From the value of LH oxidizability $k_2/(2k_4)^{1/2}$ at 50 °C equal to $0.030 \text{ M}^{-1/2} \text{ s}^{-1/2}$ in acetonitrile and $0.027 \text{ M}^{-1/2} \text{ s}^{-1/2}$ in cyclohexane (20) $2k_4$ is therefore calculated to be 3.0×10^7 and $3.6 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, respectively). For all previously investigated systems in which Class 2 hydrocarbon antioxidants exhibit strong activity, this has also meant that the rate constant for the bimolecular self-reaction of AOO $^\bullet$ radicals is much greater than that for the substrate's peroxy radicals, i.e., $2k_{30} \gg 2k_{28}$.

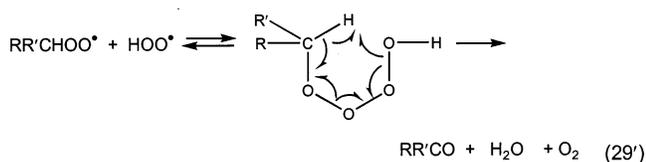


For TH, $\text{AOO}^\bullet = \text{HOO}^\bullet$, and, unlike other peroxy radicals, the magnitude of $2k_{30}$ ($= 2k_{20}$) is strongly dependent on the solvent (21b) and, in water, on the pH (28). Measured values of $2k_{20}$ at 30 °C in *n*-decane and acetonitrile are 1.3×10^9 and $8.6 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, respectively (21b). Thus, in a saturated hydrocarbon, $2k_{20} \gg 2k_4$, and it would be expected that $k_{29} \gg 2k_4$. It is therefore easy to understand why γ -terpinene behaves as a Class 2 antioxidant toward linoleic acid in cyclohexane as solvent.

That TH is also an antioxidant in acetonitrile is rather surprising because $2k_{20} \approx 2k_4$ in this solvent and k_{29} might have been expected to be of a similar order of magnitude. However, it is not only possible that $k_{29} \gg 2k_{20} \approx 2k_4$ (since cross-reactions between two unlike radicals which are faster than the bimolecular self-reactions of the two individual radicals are not uncommon (29)) but also mechanistically reasonable if reaction 29, like most (but probably not all, vide infra) other peroxy + peroxy reactions, involves initial formation of a tetraoxide followed by its decomposition (as was first proposed by Russell (30) for two secondary alkylperoxy radicals), reaction 4'.



The analogous cross-reaction between a hydroperoxyl and secondary alkylperoxy would yield water rather than an alcohol, reaction 29'.



Since the O–H bond dissociation enthalpy (BDE) is 119.3 kcal/mol for H₂O and 104.0 kcal/mol for CH₃OH, reaction 29' will be 15.3 kcal/mol more exothermic than reaction 4' (31) and with such an “extra” thermodynamic driving force would be expected to be a much faster reaction. It has been suggested that the $\text{HOO}^\bullet + \text{HOO}^\bullet$ reaction occurs via a direct “head-to-tail” hydrogen atom abstraction, reaction 20, rather than via the usual “head-to-head” tetraoxide intermediate (32). Reaction 20 will be strongly retarded in a good hydrogen bond acceptor (HBA) solvent because intermolecularly H-bonded OH groups are unreactive H-atom donors to attacking radicals (for steric reasons) (33). That is, reaction 20' will not occur and for reaction 20 to occur at least one of the HOO^\bullet radicals must be “free”, i.e., not involved in a hydrogen bond.



The foregoing implies that TH could, in principle, function as a Class 2 antioxidant toward LH even in acetonitrile. To explore this matter further, kinetic modeling was employed to confirm that the measured rates of the TH inhibited peroxidation of LH, R_{inh} , actually could be fitted to co-oxidation eq 31 (the derivation of which is given in the Supporting Information).

$$R_{\text{inh}} = \frac{k_2[\text{LH}]R_i^{1/2} + k_{32}[\text{TH}]R_i^{1/2}}{\{2k_4 + k_{29}(k_{32}[\text{TH}]/k_{33}[\text{LH}])\}^{1/2}} \quad (31)$$

In this equation R_i is the known rate of chain initiation while k_{32} and k_{33} refer to the following reactions:



The values of k_2 and $2k_4$ were based on experimental measurements at 30 °C and were set equal to 160 and $3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, respectively, at 50 °C in acetonitrile and cyclohexane (vide supra). Reaction 29 was assumed to be a nearly diffusion-controlled process and k_{29} was therefore set equal to 1×10^{10} (acetonitrile) and $3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ (cyclohexane). The values of k_{32} and k_{33} were allowed to float. Good fits of the theoretical (eq 31) and experimental data were obtained both in acetonitrile and cyclohexane (see **Figure 2** and Supporting Information).

CHD also retarded the oxidation of LH in acetonitrile and cyclohexane as is shown in **Figure 3** where, again, the solid lines were obtained by fitting to eq 31 with k_{34} replacing k_{32} and allowing k_{34} to float.



In both solvents, CHD is a somewhat less effective inhibitor of LH peroxidation than TH (see inset in **Figure 2**) because $k_{32}/k_{34} \sim 2$ in acetonitrile and cyclohexane (see captions to **Figures 2** and **3** and Supporting Information). We attribute the fact that $k_{32} > k_{34}$ to the stabilization of T^\bullet relative to CHD^\bullet by the two alkyl groups at the ends of the TH pentadienyl structure, i.e., the C–H BDE for the ring methylene groups is slightly lower in TH than in CHD.

In conclusion, the monoterpene hydrocarbon, γ -terpinene, retards the peroxidation of linoleic acid because its chain-carrying peroxy radicals are HOO^\bullet radicals which react rapidly with linoleylperoxy radicals. This antioxidant activity of γ -terpinene is comparable to that of a phenol with a $k_5 \sim (1-3) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$. However, in contrast to a phenol, this hydrocarbon (at the

concentrations explored in the current paper) does not have prooxidation effects.

ABBREVIATIONS USED

CHD, 1,4-cyclohexadiene; LH, linoleic acid; TH, γ -terpinene; AIBN, 2,2'-azobis(isobutyronitrile)

Supporting Information Available: Derivation of eq 31 and a summary table containing the rate constants used in the simulations shown in **Figures 2** and **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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