New Insight into Solvent Effects on the *Formal* $HOO^{\bullet}$ + $HOO^{\bullet}$ Reaction

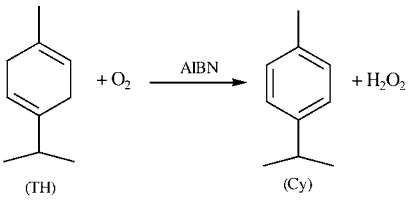
Mario C. Foti,*[a] Salvatore Sortino,[b] and K. U. Ingold[c]

Abstract: The 2,2′-azobis(isobutyronitrile)(AIBN)-induced autoxidation of γ-terpinene (TH) at 50 °C produces *p*-cymene and hydrogen peroxide in a radical-chain reaction having $HOO^{\bullet}$ as one of the chain-carrying radicals. The kinetics of this reaction in cyclohexane and *tert*-butyl alcohol show that chain termination involves the formal $HOO^{\bullet}$ + $HOO^{\bullet}$ self-reaction over a wide range of γ-terpinene, AIBN, and O_2 concentrations. However, in acetonitrile this termination process is accompanied by termination via the cross-reaction of the terpinenyl radical, $T^{\bullet}$, with the $HOO^{\bullet}$ radical under conditions of relatively high [TH] (140–1000 mM) and low $[O_2]$ (2.0–5.5 mM). This is because the formal $HOO^{\bullet}$ + $HOO^{\bullet}$ reaction is comparatively slow in acetonitrile ($2k \sim 8\times10^{7}\,M^{-1}\,s^{-1}$), whereas, this reaction is almost diffusion-controlled in *tert*-butyl alcohol and cyclohexane, $2k \sim 6.5\times10^{8}$ and $1.3\times10^{9}\,M^{-1}\,s^{-1}$, respectively. Three mechanisms for the bimolecular self-reaction of $HOO^{\bullet}$ radicals are considered: 1) a head-to-tail hydrogen-atom transfer from one radical to the other, 2) a head-to-head reaction to form an intermediate tetroxide, and 3) an electron-transfer between $HOO^{\bullet}$ and its conjugate base, the superoxide radical anion, $O_2^{-\bullet}$. The rate constant for reaction by mechanism (1) is shown to be dependent on the hydrogen bond (HB) accepting ability of the solvent; that by mechanism (2) is shown to be too slow for this process to be of any importance; and that by mechanism (3) is dependent on the pH of the solvent and its ability to support ionization. Mechanism (3) was found to be the main termination process in *tert*-butyl alcohol and acetonitrile. In the gas phase, the rate constant for the $HOO^{\bullet}$ + $HOO^{\bullet}$ reaction (mechanism (1)) is about $1.8\times10^{9}\,M^{-1}\,s^{-1}$ but in water at pH ≤ 2 where the ionization of $HOO^{\bullet}$ is completely suppressed, this rate constant is only $8.6\times10^{5}\,M^{-1}\,s^{-1}$. The very large retarding effect of water on this reaction has not previously been explained. We find that it can be quantitatively accounted for by using Abraham's HB acceptor parameter, β_2^{H}, for water of 0.38 and an estimated HB donor parameter, α_2^{H}, for $HOO^{\bullet}$ of about 0.87. These Abraham parameters allow us to predict a rate constant for the $HOO^{\bullet}$ + $HOO^{\bullet}$ reaction in water at 25 °C of $1.2\times10^{6}\,M^{-1}\,s^{-1}$ in excellent agreement with experiment.

Keywords: terpinene · autoxidation · radical reactions · radicals · solvent effects

Introduction

It has recently been reported that γ-terpinene (TH), a monoterpene present in many essential oils,[1] can function as an *effective* inhibitor of lipid peroxidation in vitro.[2,3] This is rather surprising because hydrocarbons, with a few notable exceptions,[4] are not generally able to break free radical oxidation chains. We have previously reported on the kinetics of γ-terpinene autoxidation and the mechanism by which it inhibits lipid peroxidation.[5] γ-Terpinene undergoes a slow, spontaneous, aerobic dehydrogenation by a free-radical chain mechanism. The addition of mM concentrations of the radical initiator, 2,2′-azobis(isobutyronitrile) (AIBN) strongly accelerates this reaction and the only products are *p*-cymene (Cy) and hydrogen peroxide in a 1:1 ratio [Eq. (1)].



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[a] Dr. M. C. Foti
Istituto di Chimica Biomolecolare - Sezione di Catania
Via del Santuario 110, 95028 Valverde (CT) (Italy)
Fax: (+39) 095-721-2141
E-mail: mario.foti@icb.cnr.it

[b] Dr. S. Sortino
Dipartimento di Scienze Chimiche
Università degli Studi di Catania
Viale A. Doria 8, 95125 Catania (Italy)

[c] Dr. K. U. Ingold
National Research Council
100 Sussex Drive, Ottawa, ON, K1 A0R6 (Canada)

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It has been shown by laser flash photolysis of di-*tert*-butyl peroxide in acetonitrile containing γ-terpinene (TH) at room temperature that terpinenyl ($T^{\bullet}$) and terpinenylperoxyl ($TOO^{\bullet}$) radicals are formed in the absence and presence of oxygen, respectively [Eq. (2)].[6,7]

$$\begin{aligned}&(CH_3)_3COOC(CH_3)_3 \xrightarrow{h\nu} (CH_3)_3CO^{\cdot} \xrightarrow{TH}\\ &(CH_3)_3COH + T^{\cdot} \xrightarrow{O_2} TOO^{\cdot}\end{aligned} \qquad (2)$$

The $TOO^{\bullet}$ radicals decayed with first-order kinetics by a relatively fast unimolecular elimination of $HOO^{\bullet}$[5] ($k_6 = 5\times10^4\,\text{M}^{-1}\,\text{s}^{-1}$, at room temperature) forming *p*-cymene.[6,7] Thus, $TOO^{\bullet}$ radicals are intermediates in the autoxidation of γ-terpinene but they are too short-lived ($t_{1/2} < 13.9\,\mu s$) to abstract a hydrogen atom from γ-terpinene (at $[TH] \leq 1\,\text{M}$). The chain carrier in the AIBN-initiated autoxidation of γ-terpinene (TH) is therefore $HOO^{\bullet}$[9] and the reaction mechanism has been represented as Equations (3)–(8).[5]

$$\text{AIBN} \rightarrow \xrightarrow{O_2} ROO^{\cdot}\ (\text{initiation rate} = R_i) \qquad (3)$$

$$ROO^{\cdot} + TH \rightarrow ROOH + T^{\cdot} \qquad (4)$$

$$T^{\cdot} + O_2 \rightleftharpoons TOO^{\cdot} \qquad (5)$$

$$TOO^{\cdot} \rightarrow Cy + HOO^{\cdot} \qquad (6)$$

$$HOO^{\cdot} + TH \rightarrow T^{\cdot} + H_2O_2 \qquad (7)$$

$$HOO^{\cdot} + HOO^{\cdot} \rightarrow H_2O_2 + O_2 \qquad (8)$$

Additional work has now revealed that reactions (3)–(8) do not provide a complete mechanistic description of the AIBN-initiated autoxidation of γ-terpinene under all experimental conditions. We therefore report on these new kinetic data and will also focus our discussion on the solvent effects on the rate of chain termination, reaction (8).

Results

The kinetics of the AIBN-initiated autoxidation of γ-terpinene (TH) was studied at 50 °C in acetonitrile, cyclohexane, and *tert*-butyl alcohol by monitoring the grow-in of the absorbance at 272 nm due to *p*-cymene formation (see [Eq. (1)])[13] A wide range of concentrations was employed, namely γ-terpinene (0.002–1.0 M),[12] AIBN (1–10 mM in acetonitrile and *tert*-butyl alcohol, 1–5 mM in cyclohexane) and O_2 (2–10 mM). Under all of these conditions, the rate of the non-AIBN-initiated, "spontaneous" autoxidation of γ-terpinene was negligible.[14] The measured rates of *p*-cymene formation were fitted to the general expression (I).

$$d[\text{Cy}]/dt\ [\text{M}\,\text{s}^{-1}] = C[\text{AIBN}]^a\,[\text{TH}]^b\,[O_2]^c \qquad (I)$$

The numerical factor, *C*, and the exponents *a*, *b* and *c*, are given in Table 1.

Table 1. Experimental reaction orders[a] and values[b] of *C* for the rate law for reaction (1) at 50 °C in various solvents and different concentrations ($\text{mol}\,\text{L}^{-1}$) of O_2 and γ-terpinene.[c]

Solvents	$C\times10^4$	*a*	*b*	*c*	$[TH]\times10^3$	$[O_2]\times10^3$
tert-butyl alcohol	1.1	0.42	0.90	0	2–1000	2–10
cyclohexane	0.92	0.52	0.95	0	2–1000	2–10
acetonitrile	4.4	0.52	0.95	0	1–140	2–10
acetonitrile	30	0.50	0.64	0.35	140–1000	2–5.5
acetonitrile	4.0	0.50	0.80	0	140–1000	5.5–10

[a] Error, ±10 %. [b] Error, ±≈20 %. [c] Concentration of AIBN had been varied within 1–10 mM in acetonitrile and *tert*-butyl alcohol, and 1–5 mM in cyclohexane.

Discussion

Chain-termination in the autoxidation of γ-terpinene: Kinetic analysis of reactions (3)—(8) yields the rate expression[15] II, or equivalently, III.

$$d[\text{Cy}]/dt = R_i^{1/2}\,k_7[\text{TH}]/(2k_8)^{1/2} \qquad (II)$$

$$= \frac{(2ek_d)^{1/2}k_7}{(2k_8)^{1/2}}[\text{AIBN}]^{1/2}[\text{TH}] \qquad (III)$$

The exponents (see Equation (I)) in Equation (III) are $a = 0.5$, $b = 1.0$, and $c = 0$, the last meaning that the rate of γ-terpinene autoxidation does not depend on the oxygen concentration in solution. These rate expressions (and the absence of a dependence on the oxygen partial pressure, 150–760 Torr) are consistent with our original work in cyclohexane and acetonitrile at [TH] < 140 mM.[5] They are also consistent with the present work at all AIBN, γ-terpinene, and O_2 concentrations explored for the autoxidation of γ-terpinene in cyclohexane and *tert*-butyl alcohol *and in acetonitrile provided [TH] = 1–140 mM* (see Table 1). However, these equations do not describe the autoxidation of γ-terpinene in acetonitrile at higher concentrations ([TH] = 140–1000 mM) and low oxygen concentrations (2 to 5.5 mM), where *b*, the kinetic order in [TH], decreased to 0.64, while *c*, the kinetic order in $[O_2]$, increased from 0 to 0.35 (see Table 1 and Figure 1). At higher oxygen concentrations (5.5–10 mM), *b* increased to 0.80 and *c* decreased to 0, that is, both *b* and *c* return roughly to "normal" values (see Table 1 and Figure 1).

A dependence of the rate of autoxidation of an organic substrate on the oxygen partial pressure necessarily means that not all the carbon-centered radicals are trapped by oxygen.[18] In the present case, this means that not all $T^{\bullet}$ radicals are trapped by oxygen despite the high rate constant for this addition reaction, namely,[6] $k_5 = 1.3\times10^9\,\text{M}^{-1}\,\text{s}^{-1}$. The $T^{\bullet}$ radicals must, therefore, be trapped by a second radical. Since the oxygen pressure dependence manifests itself with a relatively small change in the experimental conditions the second radical is much less likely to be another $T^{\bullet}$[18,19] than to be an $HOO^{\bullet}$ radical (see reaction (9)).

$$T^{\cdot} + HOO^{\cdot} \rightarrow Cy + H_2O_2 \qquad (9)$$

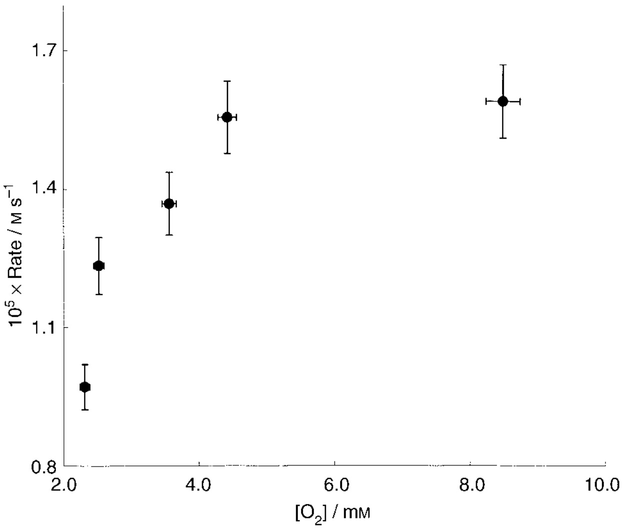


Figure 1. Rate of *p*-cymene formation in acetonitrile at 50 °C with $[TH]=0.428\,M$ and $[AIBN]=5.09\times10^{-3}\,M$ at various oxygen concentrations.

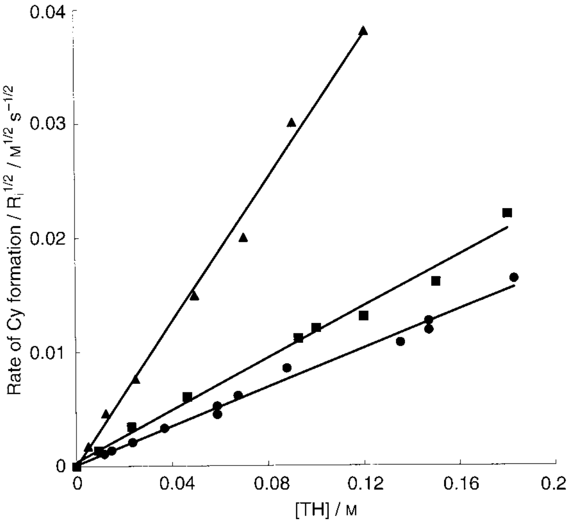


Figure 2. Representation of the rate of autoxidation of γ-terpinene at 50 °C according to the theoretical rate law given by Equation (II) in acetonitrile (▲), *tert*-butyl alcohol (■), and cyclohexane (●). The slope of the straight lines yields the value of oxidizability (in $M^{-1/2}\,s^{-1/2}$ units) of TH in the three solvents: 0.31 in acetonitrile ($R^2=0.99$), 0.11 in *tert*-butyl alcohol ($R^2=0.99$), and 0.078 in cyclohexane ($R^2=0.99$).

The participation of this cross-termination to reactions (3)—(8) changes the rate expression to Equation (IV).

$$d[Cy]/dt = R_i^{1/2} k_7[TH] \Big/ \left(2k_8 \frac{(1+k_{-5}/k_6)k_7k_9[TH]}{k_5[O_2]}\right)^{0.5} \qquad (IV)$$

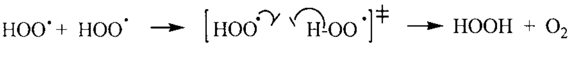
Equation (IV) reduces to Equation (II) (or (III)) at low [TH] and/or high [O$_2$] (i.e., when $2k_8 \gg (1+k_{-5}/k_6)k_7k_9[TH]/k_5[O_2]$) and to Equation (V) at high [TH] and/or low [O$_2$] (i.e., when $2k_8 \ll (1+k_{-5}/k_6)k_7k_9[TH]/k_5[O_2]$).

$$d[Cy]/dt \sim (2ek_d)^{0.5}\left(\frac{k_5k_7}{(1+k_{-5}/k_6)k_9}\right)^{0.5}[AIBN]^{0.5}[TH]^{0.5}[O_2]^{0.5} \qquad (V)$$

The autoxidation of γ-terpinene in cyclohexane and *tert*-butyl alcohol follows the "usual" kinetic expression, that is, Equation (II) (or III), under all the experimental conditions employed. Equation (II) is also followed in acetonitrile at low [TH]/[O$_2$] ratios but not at high [TH]/[O$_2$] ratios, where the kinetics approach Equation (V) (see Table 1).

Under conditions where equation II is valid the rate of reaction 1 is governed by the rate constant ratio, $k_7/(2k_8)^{0.5}$. This ratio represents the *oxidizability* of TH and can be calculated from *C* (Table 1 and from oxidation traces such as those shown in Figure 2) to be 0.078, 0.11, and $0.31\,M^{-1/2}\,s^{-1/2}$ in cyclohexane, *tert*-butyl alcohol and acetonitrile, respectively. Significant solvent effects on the rates of hydrogen atom abstraction from C–H bonds, for example, from hydrocarbons, are unknown.[20] The variations in the oxidizability of γ-terpinene in the three solvents must therefore be attributed to variations in the rate constant for chain termination, $2k_8$.

There are three *possible* mechanisms by which the *formal* HOO• radicals might self-terminate the autoxidation chains. First, a *head-to-tail* reaction in which there is hydrogen-atom abstraction from one radical by the other [Eq. (10)].[5]


$$HOO^\bullet + HOO^\bullet \longrightarrow [HOO^\bullet \cdots H\text{-}OO^\bullet]^\ddagger \longrightarrow HOOH + O_2 \qquad (10)$$

In hydrogen-bond-accepting (HBA) solvents (*S*) some HOO• radicals will form hydrogen bonds with the solvent molecules, *S*···HOO•. This will prevent two possible head-to-tail H-atom transfer reactions from occurring [Eq. (11) and (12)].

$$S\cdots HOO^\bullet + S\cdots HOO^\bullet \text{no reaction} \qquad (11)$$

$$HOO^\bullet + S\cdots HOO^\bullet \text{no reaction} \qquad (12)$$

Only the third head-to-tail reaction can occur [Eq. (13)] (see later discussion of the HOO• + HOO• reaction in water).

$$S\cdots HOO^\bullet + HOO^\bullet \rightarrow S\cdots HOOH + O_2 \qquad (13)$$

On a relative scale, the HBA abilities of solvents can best be described by the β_2^H parameters given by Abraham et al.[21] (which range in magnitude from 0.00 for saturated hydrocarbons to 1.00 for HMPA, the strongest organic HBA). The β_2^H values for cyclohexane, acetonitrile, and *tert*-butyl alcohol are:[21] 0.00, 0.44, and 0.49, respectively. If, therefore, chain termination occurred solely by reaction (10), the rate of termination would *decrease* and, hence, the oxidizability of γ-terpinene would *increase* monotonically from cyclohexane to acetonitrile to *tert*-butyl alcohol, but this is not the case (see, $k_7/(2k_8)^{0.5} = 0.078$, 0.31, and $0.11\,\text{M}^{-1/2}\,\text{s}^{-1/2}$, respectively) (see Figure 2).

Second, a *head-to-head* reaction analogous to the well-studied bimolecular self reactions of *tert*-alkylperoxyl radicals such as *tert*-butylperoxyl [Eq. (14)].

$$\begin{aligned}&ROO^{\cdot} + {}^{\cdot}OOR \rightleftharpoons ROOOOR \rightarrow [RO^{\cdot\cdot}OOOR]_{\text{cage}} \rightarrow \\ &[RO^{\cdot}O_2{}^{\cdot}OR]_{\text{cage}} \rightarrow ROOR + O_2\end{aligned} \tag{14}$$

For $R = Me_3C$, the experimental bond dissociation enthalpies (BDEs) of the central OO–OO bond and non-central O–OOO bond are about 8.5 and 17.5 $\text{kcal}\,\text{mol}^{-1}$, respectively, and the overall termination process has an activation enthalpy of about $17.5–8.5 = 9\,\text{kcal}\,\text{mol}^{-1}$ and a rate constant at 30 °C of only about $4\times10^{2}\,\text{M}^{-1}\,\text{s}^{-1}$.[22] For $R = H$, calculations have been reported which indicate BDEs of 18 and 28 $\text{kcal}\,\text{mol}^{-1}$ at 0 K for the OO–OO and O–OOO bonds, respectively.[23] Both of these BDEs are obviously too high by several $\text{kcal}\,\text{mol}^{-1}$. However, their difference is likely to be fairly reliable which would imply an overall activation enthalpy for termination by reaction (14) ($R = H$) of about 10 $\text{kcal}\,\text{mol}^{-1}$ and hence a very low rate constant for this $HOO^{\bullet}$ + $HOO^{\bullet}$ reaction pathway. Such a very slow termination step in the autoxidation of γ-terpinene can be ruled out on the basis of the rather large ($\geq 10^{7}\,\text{M}^{-1}\,\text{s}^{-1}$ at 30 °C) rate constants which have been measured for the same chain termination reaction in the autoxidation of 1,4-cyclohexadiene in organic solvents[24] and in water for the $HOO^{\bullet}$ + $HOO^{\bullet}$ reaction at low pH, namely,[25] $8.6\times10^{5}\,\text{M}^{-1}\,\text{s}^{-1}$ at room temperature (vide infra).

Third, some contribution from the known and fast ($k_{15} = 1\times10^{8}\,\text{M}^{-1}\,\text{s}^{-1}$ in water)[25] cross-reaction between $HOO^{\bullet}$ and its conjugate base, the superoxide radical anion, $O_2^{\bullet-}$ [reactions (15) and (16)].

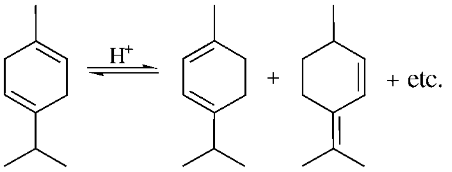
$$HOO^{\cdot} + O_2^{\cdot-} + H^{+} \rightarrow H_2O_2 + O_2 \tag{15}$$

$$HOO^{\cdot} \rightleftharpoons H^{+} + O_2^{\cdot-},\ pK_a = 4.7 \tag{16}$$

In cyclohexane, where the $HOO^{\bullet}$ radicals are not hydrogen-bonded, k_7 and $2k_8$ have been estimated to be 2800 and $1.3\times10^{9}\,\text{M}^{-1}\,\text{s}^{-1}$, respectively, at 50 °C.[5] In the other two solvents, most $HOO^{\bullet}$ radicals will be hydrogen-bonded to solvent molecules, but this is unlikely to have much effect on k_7. From the γ-terpinene oxidizabilities given above, the rate constants for chain termination can therefore be calculated to be 6.5×10^{8} and $8.2\times10^{7}\,\text{M}^{-1}\,\text{s}^{-1}$ in *tert*-butyl alcohol and acetonitrile, respectively.

Reduced termination rate constants in *tert*-butyl alcohol and acetonitrile relative to cyclohexane are consistent with the non-occurrence of reactions (11) and (12). However, the magnitudes of the rate constants in these two HBA solvents prove that hydrogen bonding is not the whole story. That is, *tert*-butyl alcohol is a stronger HBA than acetonitrile (see β_2^{H} values given above) and hence the termination rate constant would be expected, at first thought, to be smaller in *tert*-butyl alcohol than in acetonitrile, not larger. These expectations can be quantified by a more detailed approach which allows the rate constants for the chain terminating $HOO^{\bullet}$ + $HOO^{\bullet}$ processes, reactions (10) and (13), through a head-to-tail hydrogen-atom transfer, to be estimated with reasonable confidence (as is described later for the $HOO^{\bullet}$ + $HOO^{\bullet}$ reaction in water). The values obtained at room temperature are about $1.9\times10^{5}\,\text{M}^{-1}\,\text{s}^{-1}$ in *tert*-butyl alcohol and about $4.5\times10^{5}\,\text{M}^{-1}\,\text{s}^{-1}$ in acetonitrile, values which probably increase by about a factor of 2 at 50 °C.[26] Although the validity of these two estimated rate constants cannot be independently checked, the same procedure applied to water yields a rate constant in excellent agreement with the value measured at room temperature and low pH where reaction (15) has been completely suppressed (see below). The rate constants calculated in this way for reaction (13) in *tert*-butyl alcohol and acetonitrile are orders of magnitude smaller than the values calculated for chain-termination from the γ-terpinene oxidizabilities in these two solvents, namely 6.5×10^{8} and $8.2\times10^{7}\,\text{M}^{-1}\,\text{s}^{-1}$, respectively. This must mean that there is considerable ionization of $HOO^{\bullet}$ (pK_a 4.7, reaction (16)) both in *tert*-butyl alcohol and acetonitrile, and hence a significant contribution to chain termination from reaction (15). This is consistent with the fact that phenols with pK_a values of about 10 are partially ionized in alcohols[27,28] and that a compound with an α–γ-keto–enol moiety (pK_a 7.9) is not only partially ionized in alcohols but is also partially ionized in ethyl acetate ($\varepsilon = 6.0$) though not in 1,4-dioxane ($\varepsilon = 2.2$).[29] That the much stronger acid, $HOO^{\bullet}$, should be partially ionized in *tert*-butyl alcohol ($\varepsilon = 17.7$) and acetonitrile ($\varepsilon = 35.9$) is therefore to be expected. The eightfold larger rate constant for chain termination in *tert*-butyl alcohol than in acetonitrile can be attributed to the better abilities of hydroxylic solvents to support ionization of Brønsted acids.

The partial ionization of phenols in alcohols dramatically accelerated the rates of their reactions with the stable free radical, 2,2-diphenyl-1-picrylhydrazyl, $dpph^{\bullet}$, because electron transfer from phenoxide anions to $dpph^{\bullet}$ is very much faster than hydrogen-atom transfer from the neutral phenols.[27–29] The already high rate constants in alcoholic solvents could be dramatically increased by the addition of small quantities of a strong base such as sodium methoxide.[27,29] However, all $dpph^{\bullet}$ rate enhancements in alcohols could be completely eliminated by the addition of acetic acid[27–29] (pK_a 4.75). In the present case, the addition of 150 μL of KOH-saturated *tert*-butyl alcohol to γ-terpinene/AIBN in 2 mL *tert*-butyl alcohol produced an 11-fold reduction in rate with the oxidizability dropping to $0.01\,\text{M}^{-1/2}\,\text{s}^{-1/2}$. This means, of course, that the chain termination rate constant had *increased* by a factor of $(11)^2$, that is, by a factor of 121, owing to a shift in equilibrium (16) towards superoxide and the enhanced importance of the fast reaction (15).[30] Similar, but less dramatic results were obtained in acetonitrile where the addition of 100 μL of KOH-saturated CH_3CN to γ-terpinene/AIBN in 2 mL CH_3CN reduced the rate by a factor of 2, implying a fourfold increase in the termination rate constant. The rate of autoxidation of γ-terpinene was not increased by the addition of acetic acid (up to 1 M),[31] a result that we attribute to the very similar pK_a values of this acid and the HOO$^•$ radical. Unfortunately, the addition of the much stronger acid, CF_3COOH, caused a rapid increase in the 272 nm absorbance of the γ-terpinene solution even in the absence of AIBN[32] because it isomerized γ-terpinene (via carbocation intermediates) to conjugated dienes (reaction (17)), which absorb strongly in the ultraviolet.[33]



(17)

To conclude this section, the oxygen pressure dependence on reaction (1) was observed only in acetonitrile and only when [TH] > 140 mM *and* [O_2] < 5.5 mM. This result is consistent with the relatively low rate constant (8×10^7 M^{-1} s^{-1})[5] found for chain termination in this solvent at low [TH] and high [O_2], where termination involves reactions (10), (13), and (15). Because these chain termination processes taken together are relatively slow, the diffusion-controlled T$^•$ + HOO$^•$ cross-termination (reaction (9)) can become significant under appropriate experimental conditions.

Role of intermolecular hydrogen bonding in the HOO$^•$ + HOO$^•$ reaction in water: The rate constant for the HOO$^•$ + HOO$^•$ reaction in the gas phase at 25 °C and 1 atm pressure of an inert gas is about 3×10^{-12} cm^3 molecule^{-1} s^{-1},[34] that is, about 1.8×10^9 M^{-1} s^{-1}. The chain-carrying peroxyl radical in the autoxidation of 1,4-cyclohexadiene is the HOO$^•$ radical and in the non-HBA solvent, *n*-decane ($\beta_2^H = 0.00$), at 30 °C the rate constant for the chain terminating HOO$^•$ + HOO$^•$ reaction is 1.34×10^9 M^{-1} s^{-1},[10] a value close to that found in the gas phase and close to the diffusion-controlled limit. In water, the *formal* HOO$^•$ + HOO$^•$ reaction rate constant shows an interesting pH-dependence increasing from < 1 M^{-1} s^{-1} at pH 13 to a maximum of 3×10^7 M^{-1} s^{-1} at pH 4.7 and then falling to 8.6×10^5 M^{-1} s^{-1} from pH 2 to pH 0.[25] These changes have been explained on the basis of the relative concentration of HOO$^•$ and its conjugate base, $O_2^{•-}$, at the different pH values ([Eq. (16)]). At high pH only $O_2^{•-}$ is present and, if these radical anions do react with one another, the reaction is exceedingly slow ($2k < 0.35$ M^{-1} s^{-1}).[25] As the pH is reduced from 13, the cross-reaction (15) (HOO$^•$ + $O_2^{•-}$) becomes increasingly important ($k_{15} = 1\times10^8$ M^{-1} s^{-1})[25] and the measured rate constant reaches its maximum value at pH 4.7, the pK_a value of HOO$^•$. At pH 2 and lower, only HOO$^•$ is present and the *true* HOO$^•$ + HOO$^•$ reaction is rather slow (8.6×10^5 M^{-1} s^{-1}). This picture explains the observed pH-dependence of the formal HOO$^•$ + HOO$^•$ reaction but it does *not* explain why the true HOO$^•$ + HOO$^•$ reaction is so slow in water. To our knowledge, this subject has not been previously addressed. We show that the slow HOO$^•$ + HOO$^•$ reaction can be accounted for both *qualitatively and quantitatively* in terms of hydrogen bond formation involving HOO$^•$ as the hydrogen bond donor and H_2O as the hydrogen bond acceptor ([Eq. (18) and (19)]).

$$H_2O + HOO^\cdot \rightleftharpoons H_2O \cdots HOO^\cdot \tag{18}$$

$$H_2O \cdots HOO^\cdot + HOO^\cdot \rightarrow H_2O + H_2O_2 + O_2 \tag{19}$$

The rate constant, k_{19}, can be predicted[35] using the well-established equation (VI),[20c,40] which quantifies the kinetic solvent effects (KSEs) on the hydrogen-atom transfer from phenols and other substrates, XH, to *any* free radical (Y$^•$), where $k^0_{XH/Y^\cdot}$ is the rate constant in a saturated hydrocarbon solvent ($\beta_2^H = 0.00$), $k^S_{XH/Y^\cdot}$ is the measured rate constant in an HBA solvent, *S*, α_2^H is the HB donating ability of XH[37] and β_2^H the HB accepting ability of *S*.[21]

$$\log k^S_{XH/Y^\cdot} = \log k^0_{XH/Y^\cdot} - 8.3\alpha_2^H\beta_2^H \tag{VI}$$

The *formal* HOO$^•$ + HOO$^•$ reaction in water at pH ≤ 2 occurs solely by reaction (19) and its rate constant can be calculated by using the measured rate constant for reaction (8) in *n*-decane (divided by 2),[39] namely[24] $2k_8/2 = 1.34\times10^9/2 = 6.7\times10^8$ M^{-1} s^{-1}, the known[21] β_2^H for water of 0.38 provided an α_2^H value for the HOO$^•$ radical can be estimated. This estimate was made using the pK_a values and α_2^H values for three strong, monohydroxylic, acids (i.e., *not* carboxylic acids). These three compounds, their pK_a values,[41] and α_2^H[37] values were: 3-cyanophenol, 8.57, 0.77; 3-nitrophenol, 8.36, 0.79 and 4-nitrophenol, 7.15, 0.824. A linear extrapolation of a plot of these pK_a values versus α_2^H values to the pK_a of HOO$^•$ (4.7) yields an α_2^H value for HOO$^•$ of 0.87, a value which appears reasonable since even the very strong acid, CCl_3CO_2H (pK_a = 0.51) has an α_2^H value of only 0.95.[42] At all events, applying an α_2^H value of 0.87 to Equation (VI) yields an estimated rate constant k_{19}^{calcd} of 1.2×10^6 M^{-1} s^{-1}, in excellent agreement with the experimental value $k_{19} = 0.86\times10^6$ M^{-1} s^{-1}).[25] This agreement further confirms our earlier conclusions[20c] that KSEs in free radical hydrogen-atom abstraction reactions can be *quantitatively* accounted for by using the α_2^H and β_2^H parameters developed by Abraham et al. and extends the scope of Equation (VI) in the prediction of KSEs on hydrogen-atom transfers between radicals.

Experimental Section

Materials and instruments: γ-Terpinene (95 %) was purchased from Fluka, distilled at reduced pressure and stored under nitrogen at −20 °C. AIBN, from Merck (98 %), was recrystallized from methanol and stored at −20 °C. All solvents (Aldrich) were of HPLC grade and were used as received. The kinetics were monitored on a Perkin-Elmer Lambda 25 UV/VIS double ray spectrophotometer; the GC-MS analyses were carried out on a Hewlett-Packard 5890 instrument interfaced to a Hewlett-Packard 5971 A Mass Selective Detector (DB-5 capillary column, 30 m × 0.25 mm, film thickness 0.25 μm). Finally, HPLC-UV-DAD analyses of solutions containing γ-terpinene and CF_3COOH were done on a Waters Instrument model 1525 connected with Waters model 996 PDA detector (column: Phenomenex Luna, C18 250 × 4.6 mm (5 μm) at 20 °C using as eluent system H_2O/CH_3CN).

Peroxidation of γ-terpinene: Solutions of γ-terpinene and AIBN at various concentrations in the solvent in use were mixed 1:1 (v/v) in a UV cuvette saturated with O_2/N_2 mixtures (prepared with a gas mixer system), hermetically sealed, and quickly heated to 50 °C. Thereafter, the cell compartment was maintained at 50 °C and the absorbance at 272 nm was monitored over time as previously described.[5] Excellent straight lines ($R^2 = 0.97$–0.99) of absorbance versus time were usually obtained, whose slopes (divided by the value of ε_{272}) gave the initial rate of reaction, $d[\text{Cy}]/dt$ in $\text{M}\,\text{s}^{-1}$ units. UV cells of 1, 0.5, and 0.1 cm optical path were used according to the initial absorbance of the solution.[12] The reaction orders for AIBN, γ-terpinene, and O_2 were obtained by changing the concentration of the pertinent species while keeping the others constant.

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[7] Two different $\text{T}^{\bullet}$ radicals are formed by hydrogen-atom abstraction from γ-terpinene CH_2 groups and these can form, four different peroxyl radicals with conjugated double bonds and two with non-conjugated double bonds. These last two radicals probably undergo extremely rapid reversion to $\text{T}^{\bullet}$ and O_2.[6,8]

[8] D. A. Pratt, J. H. Mills, N. A. Porter, *J. Am. Chem. Soc.* **2003**, *125*, 5801–5810 and references therein.

[9] The similarity between reaction (1) and the autoxidation of 1,4-cyclohexadiene to form benzene and hydrogen peroxide,[10] the ability of γ-terpinene to retard the autoxidation of linoleic acid,[5] and the abilities of $FeCl_3$ and $CuCl_2$ to retard γ-terpinene autoxidation[11] also support the conclusion that $\text{HOO}^{\bullet}$ is the chain carrier.

[10] J. A. Howard, K. U. Ingold, *Can. J. Chem.* **1967**, *45*, 785–792.

[11] M. C. Foti, K. U. Ingold, *J. Org. Chem.* **2003**, *68*, 9162–9165 .

[12] Although γ-terpinene was carefully distilled, it contained significant quantities of *p*-cymene which precluded the spectrophotometric method for monitoring γ-terpinene autoxidation at $[\text{TH}] > 1\,\text{M}$.

[13] For *p*-cymene in *tert*-butyl alcohol at 50 °C, $\varepsilon\ (272\,\text{nm}) = 500\,\text{M}^{-1}\,\text{cm}^{-1}$. The ε values in acetonitrile and cyclohexane and further experimental details have been reported in reference [5].

[14] "Spontaneous", oxygen-induced autoxidation of neat γ-terpinene at 50 °C under air occurs with a rate of about $10^{-8}\,\text{M}\,\text{s}^{-1}$ which is more than 100 times slower than the rates of the AIBN-initiated autoxidation at much lower γ-terpinene concentrations. Interestingly, the spontaneous autoxidation gave a very minor amount (~3 % of the yield of *p*-cymene) of 1,2,4,5-tetrahydroxy-1-isopropyl-4-methylcyclohexane. The properties of this unusual product and the mechanism by which it is formed will be reported later.

[15] The rate of initiation is $R_i = 2ek_d[\text{AIBN}]$, where k_d is the rate constant for thermal decomposition of AIBN and e represents the fraction of geminate radical pairs that diffuse out of the solvent cage in which they are produced. Values of $2ek_d$ (in s^{-1}) at 50 °C are: 1.3×10^{-6} in cyclohexane,[16] 2.0×10^{-6} in acetonitrile,[16] and about 2.5×10^{-6} in *tert*-butyl alcohol.[17]

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[17] Although not directly reported, the mean value $2ek_d = 2.5 \times 10^{-6}\,\text{s}^{-1}$ in *tert*-butyl alcohol at 50 °C can be calculated from data in: a) M. Lucarini, G. F. Pedulli, L. Valgimigli, *J. Org. Chem.* **1998**, *63*, 4497–4499; b) P. Pedrielli, L. M. Holkeri, L. H. Skibsted, *Eur. Food Res. Technol.* **2001**, *213*, 405–408.

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[19] Because of the fast reaction of dioxygen with $\text{T}^{\bullet}$ [reaction (5)], it is obvious that the steady-state concentration of $\text{T}^{\bullet}$ will be much lower than that of $\text{HOO}^{\bullet}$.

[20] a) D. V. Avila, C. E. Brown, K. U. Ingold, J. Lusztyk, *J. Am. Chem. Soc.* **1993**, *115*, 466–470; b) L. Valgimigli, K. U. Ingold, J. Lusztyk, *J. Org. Chem.* **1996**, *61*, 7947–7950; c) D. W. Snelgrove, J. Lusztyk, J. T. Banks, P. Mulder, K. U. Ingold, *J. Am. Chem. Soc.* **2001**, *123*, 469–477; d) L. Zhang, J. Cradlebaugh, G. Litwinienko, B. E. Smart, K. U. Ingold, W. R.Dolbier Jr., *Org. Biomol. Chem.* **2004**, *2*, 689–694.

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[26] Assuming that the Arrhenius preexponential factor for these radical–radical reactions is about $10^9\,\text{M}^{-1}\,\text{s}^{-1}$, the room-temperature rate constants imply that E_a is about $5\,\text{kcal}\,\text{mol}^{-1}$, which would produce a roughly twofold increase in the rate constants at 50 °C. This $5\,\text{kcal}\,\text{mol}^{-1}$ activation enthalpy can be assigned to the enthalpy of formation of the hydrogen bond between the $\text{HOO}^{\bullet}$ radical and these HBA solvents.

[27] G. Litwinienko, K. U. Ingold, *J. Org. Chem.* **2003**, *68*, 3433–3438.

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[29] G. Litwinienko, K. U. Ingold, *J. Org. Chem.* **2004**, *69*, 5888–5896.

[30] The 120-fold increase in the termination rate constant may be a slight overestimate since more $O_2^{\bullet -}$ means less $\text{HOO}^{\bullet}$ and hence less chain propagation because $O_2^{\bullet -}$ cannot abstract a hydrogen atom from γ-terpinene.

[31] High concentrations of acetic acid produced a small decrease in the rate of γ-terpinene autoxidation. This reduction was shown not to be due to a change in the rate of initiation, R_i, since the rates of disappearance of hydroquinone ($6.45 \times 10^{-4}\,\text{M}$) in oxygenated acetonitrile at 50 °C containing AIBN ($1.31 \times 10^{-2}\,\text{M}$) were the same in the presence of 0.9 M AcOH as in the absence of acid, namely, 2.46×10^{-8} and $2.40 \times 10^{-8}\,\text{M}\,\text{s}^{-1}$, respectively.

[32] Addition of 150 μL of CF_3CO_2H ($[CF_3CO_2H] = 0.94\,\text{M}$) to 2.0 mL of a 60 mM γ-terpinene solution at 50 °C caused an increase of the absorbance at 272 nm of about 0.006 units per second. When the quantity of CF_3CO_2H was reduced to 20 μL ($[CF_3CO_2H] = 0.125\,\text{M}$), the absorbance increased to a rate of about 3×10^{-4} units per second. After adding AIBN to a final concentration of 3.2 mM, this rate further increased to 1.3×10^{-3} units per second. In the absence of CF_3CO_2H, the rate of AIBN-induced peroxidation of γ-terpinene was about 1.0×10^{-3} absorbance units per second.

[33] 1,3-Cyclohexadiene has an absorption band at 259 nm and $\varepsilon_{max} = 3200\,\text{M}^{-1}\,\text{cm}^{-1}$. Exocyclic conjugated dienes are characterized by $\lambda_{max} < 259$ nm and $\varepsilon_{max} > 3 \times 10^3\,\text{M}^{-1}\,\text{cm}^{-1}$.[16]

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[35] An alternative and independent approach to the calculation of k_{19} is to use the equation developed by Abraham et al.[36] that relates the equilibrium constants, K, for the formation of 1:1 HB complexes in CCl_4 at room temperature between HBDs and HBAs to their respective α_2^{H}[37] and β_2^{H} values: $\log (K/\mathrm{M}^{-1}) = 7.354\ \alpha_2^{H}\beta_2^{H} - 1.094$. Such equilibrium constants appear to be essentially independent of the solvent;[20c,38] application to equilibrium (18) using an α_2^{H} value for $HOO^{\bullet}$ of 0.87 (see Discussion) and the known[21] β_2^{H} value for water of 0.38 yields a K equal to $22\,\mathrm{M}^{-1}$. Since neat water is about 55 M, the fraction of non-HB $HOO^{\bullet}$ radicals, $f_{HOO^{\bullet}}$, is given by $1/(22 \times 55) = 8.3 \times 10^{-4}$. The predicted rate constant for reaction (19) will therefore be the rate constant measured for reaction (8) in the non-HBA solvent, *n*-decane, namely[24] $2k_8 = 1.34 \times 10^{9}\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$, divided by 2,[39] and multiplied by $f_{HOO^{\bullet}}$, that is, $6.7 \times 10^{8} \times 8.3 \times 10^{-4} = 5.6 \times 10^{5}\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$.

[36] M. H. Abraham, P. L. Grellier, D. V. Prior, R. W. Taft, J. J. Morris, P. J. Taylor, C. Laurence, M. Berthelot, R. M. Doherty, M. J. Kamlet, J.-L. M. Abboud, K. Sraidi, G. Guihéneuf, *J. Am. Chem. Soc.* **1988**. *110*, 8534–8536.

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