## Reactive Oxygen Species

# Hydroperoxyl Radicals (HOO<sup>•</sup>): Vitamin E Regeneration and H-Bond Effects on the Hydrogen Atom Transfer

Jakub Cedrowski,<sup>[a]</sup> Grzegorz Litwinienko,\*<sup>[a]</sup> Andrea Baschieri,<sup>[b]</sup> and Riccardo Amorati\*<sup>[b]</sup>

**Abstract:** Hydroperoxyl (HOO') and alkylperoxyl (ROO') radicals show a different behavior in H-atom-transfer processes. Both radicals react with an analogue of  $\alpha$ -tocopherol (TOH), but HOO', unlike ROO', is able to regenerate TOH by a fast H-atom transfer: TO' + HOO'  $\rightarrow$  TOH + O<sub>2</sub>. The kinetic solvent effect on the H-atom transfer from TOH to HOO' is much stronger than that observed for ROO' because noncovalent interactions with polar solvents (Solv--HOO') destabilize the transition state.

Hydroperoxyl radicals (HOO') are mediators of many processes of wide current interest, such as atmospheric pollutant degradation,<sup>[1]</sup> photocatalysis,<sup>[2]</sup> and molecular oxygen activation on metal surfaces<sup>[3]</sup> or in enzymes.<sup>[4]</sup> While its conjugated base (superoxide, O2.) is inactive as an oxidizer,<sup>[5]</sup> HOO is a source of oxidative damage in biological systems. Its formation is related to degenerative pathologies and aging.<sup>[6]</sup> HOO' is believed to be essentially similar to alkylperoxyl radicals in H-atom transfer (HAT) reactions.<sup>[6,7]</sup> The HOO-H bond dissociation enthalpy (BDE) is slightly higher (87.5 kcal mol<sup>-1</sup>, gas phase)<sup>[7]</sup> than the BDE of ROO-H ( $\approx$ 85 kcalmol<sup>-1</sup>, gas phase).<sup>[7]</sup> On the other hand, the knowledge about reducing properties of HOO' is still very limited. The hydroperoxyl radical has an exceptionally weak H-OO' BDE (49.2 kcal mol-1),[7] which allows us to consider HOO' as potentially good H-atom donating agent. Despite the great role of the HOO'/ $O_2$ ' pair in biology, the study of the HOO' reactivity with phenolic antioxidants has been somewhat neglected,<sup>[7]</sup> mainly because this radical is hard to be generated in solution in experimental systems and its reactivity is very difficult to be followed by common spectroscopic methods.<sup>[8]</sup> To address this lack of knowledge, we studied the reaction of HOO' with 2,2,5,7,8-pentamethyl-6-chromanol (TOH), an analogue of  $\alpha$ -tocopherol (the main component of vitamin E), by following the autoxidation rate of 1,4-cyclohexadiene (CHD) in different organic solvents. In our system, HOO' exists exclusive-

[a] J. Cedrowski, Prof. G. Litwinienko	
Faculty of Chemistry, University of Warsaw	
Pasteura 1, 02-093 Warsaw (Poland)	
E-mail: litwin@chem.uw.edu.pl	

- [b] Dr. A. Baschieri, Dr. R. Amorati Department of Chemistry "G. Ciamician", University of Bologna Via S. Giacomo 11, 40126 Bologna (Italy) E-mail: riccardo.amorati@unibo.it
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ly in the protonated form and the presence of superoxide can be neglected. Autoxidation of CHD to benzene is a well-known chain process, in which HOO' acts as propagating radical (see Scheme 1 and Figure 1).<sup>[9]</sup>

AIBN 
$$\xrightarrow{O_2}$$
 R<sup>1</sup>OO<sup>•</sup>  
R<sup>1</sup>OO<sup>•</sup> +  $() \longrightarrow$  R<sup>1</sup>OOH +  $()$   
 $() + O_2 \longrightarrow$   $() \longrightarrow$  HOOH +  $()$   
HOO<sup>•</sup> +  $() \longrightarrow$  HOOH +  $()$   
2 HOO<sup>•</sup> → H<sub>2</sub>O<sub>2</sub> + O<sub>2</sub>

**Scheme 1.** Autoxidation mechanism of 1,4-cyclohexadiene<sup>[9]</sup> initiated by AIBN (2,2'-azobis(isobutyronitrile));  $R^1 = (CH_3)_2(CN)C$ .



**Figure 1.** Oxygen consumption measured during autoxidation experiments in chlorobenzene initiated by AIBN (0.05 m) at 30 °C with the following reactants: a) styrene (2.1 m); b) CHD (cyclohexadiene, 0.26 m); c) styrene (2.1 m) and TOH (5  $\mu$ m); d) CHD (0.26 m) and TOH (6.2  $\mu$ m). The points are the numerical fitting of trace d.

In the presence of TOH the rate of the CHD autoxidation, measured as the rate of  $O_2$  consumption, was slowed down (Figure 1 b, d) because of the trapping of HOO<sup>•</sup> by TOH [Eq. (1)].

$$\mathsf{TOH} + \mathsf{HOO}^{\bullet} \xrightarrow{k_1} \mathsf{TO}^{\bullet} + \mathsf{HOOH}$$
(1)

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To compare the chemistry of HOO<sup>•</sup> and ROO<sup>•</sup> radicals, the rate of the reaction of styrylperoxyl with TOH [Eq. (2)] was also determined by studying the autoxidation of styrene (Figure 1 a, c).<sup>[10]</sup>

$$\mathsf{TOH} + \mathsf{ROO}^{\bullet} \xrightarrow{\kappa_2} \mathsf{TO}^{\bullet} + \mathsf{ROOH}$$
(2)

The chain-breaking effect of TOH was more clearly visible in styrene, because this substrate has a lower propagation rate constant than CHD (41<sup>[11]</sup> vs. 1400<sup>[9]</sup> M<sup>-1</sup>s<sup>-1</sup> in chlorobenzene, respectively). In CHD, however, the length of the inhibition period was up to 10 times longer (corresponding to  $\approx$  20 radicals guenched by each TOH molecule) than in styrene. Analysis of the products formed in the mixture of TOH, AIBN (2,2'-azobis-(isobutyronitrile)), and CHD in the presence of O<sub>2</sub> (Figure 1S in the Supporting Information) showed that in such system HOO' acts as the propagating radical (no products were formed by reaction of TOH with peroxyl radicals derived from AIBN) and that TOH was consumed more slowly than expected, suggesting that HOO' may reduce TO' radicals. This double-faced behavior of HOO' was confirmed by performing autoxidation experiments (in PhCl) in the presence of 3,5-di-tert-butyl-orthoquinone. In styrene, this compound did not modify the rate of the O<sub>2</sub> uptake, as expected from the absence of phenolic OH groups. However, when CHD was oxidized instead of styrene, a strong inhibition was observed and this effect can be only explained as originating from the reduction of the orthoguinone by HOO<sup>•</sup> (see Figure 2S in the Supporting Information for details).<sup>[12]</sup> Therefore, the unusual stoichiometric factor of the TOH inhibition of the CHD autoxidation can be attributed to the reduction of TO' by HOO'. Based on BDE values for H-OO' and TO–H (49.2 $^{[7]}$  and 77.1 $^{[13]}$  kcal mol $^{-1}$ , respectively), this reaction is substantially exothermic ( $\Delta H^{\circ} \approx -28 \text{ kcal mol}^{-1}$ ). With this thermodynamic justification, a competition between the addition  $(k_{3a})^{[14]}$  and reduction  $(k_{3b})$ , can be reasonably proposed (Scheme 2).



Scheme 2. Different reaction pathways between hydroperoxyl radicals (HOO') and  $\alpha$ -tocopheroxyl radicals (TO').

The autoxidation plots were subsequently analyzed by a kinetic simulation software by taking into account the two possible pathways for the TO' decay, reactions 3 a and 3 b (Scheme 2).<sup>[15]</sup> A very good fitting of the experimental  $O_2$  traces was obtained in all the investigated solvents (see for in-

stance Figure 1d for PhCl). Since the propagation and termination rate constants of CHD and styrene are known (see the Supporting Information for the kinetic details),<sup>[9]</sup> the values of  $k_{1}$ ,  $k_{2}$ , and the  $k_{3b}/k_{3a}$  ratio could be obtained (see Table 1).

<b>Table 1.</b> Rate constants for the reaction of TOH with hydroperoxyl $(k_1)$ or with styrylperoxyl $(k_2)$ radicals and competition between reduction and oxidation of TO <sup>•</sup> by HOO <sup>•</sup> radicals $(k_{3b}/k_{3a})$ .				
Solvent $(\beta_2^{H})^{[a]}$	$k_1 \; [\mathrm{m}^{-1}  \mathrm{s}^{-1}]$	k <sub>2</sub> [м <sup>-1</sup> s <sup>-1</sup> ]	$k_{\rm 3b}/k_{\rm 3a}$	
CCl <sub>4</sub> (0.00) PhCl (0.09) Dioxane <sup>[b]</sup> (0.41)	$(1.6 \pm 0.4) \times 10^7$ $(1.6 \pm 0.1) \times 10^6$ $(1.1 \pm 0.1) \times 10^5$	$(4.0 \pm 0.4) \times 10^{6}$ $(2.7 \pm 0.3) \times 10^{6}$ $(5.0 \pm 0.1) \times 10^{5}$	$9.9 \pm 3.5$ $8.3 \pm 0.5$ $5.2 \pm 0.9$	
MeCN (0.44) THF <sup>[b]</sup> (0.51)	$(6.8 \pm 0.7) \times 10^4$ $(2.5 \pm 0.5) \times 10^4$	$(6.8 \pm 0.6) \times 10^{5}$ $(6.2 \pm 1.0) \times 10^{5}$	$2.2 \pm 1.0 \\ 0.5 \pm 0.1$	
[a] From ref. [17b]. [b] Co-oxidation of the solvent was also considered, see the Supporting Information.				

The data presented in Table 1 indicate that in a non-H-bondaccepting solvent like CCl<sub>4</sub> the HOO' radical is about four times more reactive than ROO' towards TOH, in agreement with the larger BDE for HOO-H than for ROO-H. In chlorobenzene, the reactivity of HOO' is halved compared to that of ROO', while it becomes 1/25 in THF. The different susceptibility of these two radicals on the kinetic solvent effect (KSE) is in contrast to the general assumption that the decrease of the rate constant for an H-atom transfer  $(k^{S})$  from a phenol to a radical depends only on the ability of a phenol to form a H-bond with an Hbond-accepting solvent.<sup>[16a-d]</sup> Thus,  $k^{s}$  in any solvent can be correlated with the rate constant in a non-H-bonding solvent  $k^0$  via Equation (3),<sup>[16a]</sup> in which  $\alpha_2^{H}$  and  $\beta_2^{H}$  represent the relative ability of the substrate to donate an H-bond (range 0 to 1.0)  $^{\left[ 17a\right] }$  and the relative ability of the solvent to accept a Hbond (range 0 to 1.0), respectively.<sup>[17b]</sup>

$$\log(k^{\rm S}\,{\rm M}^{-1}\,{\rm s}^{-1}) = \log(k^{\rm 0}\,{\rm M}^{-1}\,{\rm s}^{-1}) - 8.3\,\alpha_2^{\rm H}\,\beta_2^{\rm H} \tag{3}$$

According to Equation (3), the magnitude of the KSE does not depend on the nature of the abstracting radical,<sup>[16a]</sup> as depicted by pathways a and b in Scheme 3.

The KSE mechanism holds for organic radicals, such as alkoxyl, alkyl, alkylperoxyl, and hydrazyl radicals in almost any solvent,<sup>[16a-d]</sup> with a few exceptions.<sup>[16d,e,18]</sup> If the logarithm of the rate constants for the reaction of TOH with ROO', tBuO',<sup>[16a]</sup> and 2,2'-diphenylpicrylhydrazyl (dpph')<sup>[16b]</sup> radicals is plotted as a function of the solvent parameter  $\beta_2^{\text{H}}$  (Figure 2), nearly parallel straight lines are observed in agreement with Equation (3).<sup>[19]</sup> A much bigger slope for the HOO' line indicates that the reaction of TOH with the HOO' radicals has a stronger KSE than predicted by Equation (3).

The solvents used in our experiments allowed us to exclude a deprotonation equilibrium (HOO<sup>•</sup> $\Rightarrow$ H<sup>+</sup> + O<sub>2</sub><sup>•-</sup>), which may diminish the concentration of HOO<sup>•</sup> radicals in the system, because dioxane and THF are not ionization-supporting solvents.<sup>[16d]</sup> Linearity of the log( $k_1$ ) versus  $\beta_2^{\text{H}}$  relationship (Figure 2), in opposition to the scattered dependence between

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**Scheme 3.** Reaction between HOO<sup>•</sup> and TOH in the presence of an H-bond-accepting solvent (S). The S···HOO<sup>•</sup> complex is less reactive than HOO<sup>•</sup> ( $k_{SHOO} < k_{HOO}$ ).

log( $k_1$ ) and the dielectric constant (see Figure 3S in the Supporting Information), indicates a prominent role of the H-bond formed between HOO' and the solvent. Therefore, the most probable justification of the anomalous KSE of HOO' in respect to ROO' is that some solvents, besides accepting the H-bond from TOH, also interact with HOO' by forming a S···HOO' complex that is less reactive than free HOO' (shown by reactions c and d in Scheme 3). The decrease of reactivity of the H-bonded HOO' is indeed a general characteristic of this radical. Also the logarithm of the rate constant for its reaction with CHD, measured by Howard and Ingold, and by Sawyer et al.,<sup>[9]</sup> gives excellent straight lines when plotted against the  $\beta_2^{H}$  of the solvent (see Figure 4S in the Supporting Information).

The effect of the S…HOO' complex formation on the H-atom abstraction was further investigated by computational meth-



**Figure 2.** The kinetic solvent effect observed for the reaction of TOH with tBuO<sup>•</sup> ( $\triangle$ ), ROO<sup>•</sup> ( $\bigcirc$ ), dpph<sup>•</sup> (2,2'-diphenylpicrylhydrazyl,  $\bigtriangledown$ ), and HOO<sup>•</sup> ( $\bigcirc$ ) in CCl<sub>4</sub>, PhCl, MeCN, dioxane, and THF. The slopes are -1.5, -1.8, and -2.0 for tBuO<sup>•</sup>, ROO<sup>•</sup>, and dpph<sup>•</sup>, respectively. For TOH reacting with HOO<sup>•</sup> the slope is -5.0.

ods (see details in the Supporting Information).<sup>[20]</sup> The reaction was modelled by using (non solvated) phenol and HCN as analogues of TOH and acetonitrile, respectively. In Figure 3 it is shown that the HCN···HOO' interaction makes the HAT reaction more endothermic by 4.6 kcal mol<sup>-1</sup> and increases the activation energy by 2.6 kcal mol<sup>-1</sup> compared to free HOO' as H-atom abstracting radical. Interestingly, in the HCN···HOO' complex the length of the H-bond increases during the reaction



Figure 3. Reaction of HOO' with phenol, with or without HCN as H-bond acceptor in the S-HOO' complex, at the M05/6-311 g(2df,2p) level of theory. The length of the H-bond is indicated.

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pathway (Figure 3), which indicates that this interaction becomes weaker when passing from the reactants to the products. This clearly implies that HOO' is a much better H-bond donor than HOOH towards HCN. In homogeneous series of compounds, the H-bond donating ability is usually proportional to the acidity,<sup>[21]</sup> therefore  $H_2O_2$  with its pK<sub>a</sub> of 11.6 is a considerably weaker acid than HOO<sup>•</sup> ( $pK_a = 4.7$ ).<sup>[7]</sup> This explanation agrees with the known ability of HOO' to donate H-bonds to water and organic polar molecules.<sup>[1,21,22]</sup> A similar reactivity decrease occurs in general when the stabilization of a radical is stronger in the reactants than in the transition state.<sup>[23]</sup>

From Table 1, it can also be seen that the  $k_{3b}/k_{3a}$  ratio decreases 20 times when passing from CCl<sub>4</sub> to THF. This can be explained by the inability of the H-bonded complex S-HOO' to reduce TO' (Scheme 2, reaction 3b), while reaction 3a should be less dependent on the solvent. Considering that the rate constant of the phenoxyl-alkylperoxyl recombination is usually high  $(\approx 10^8 \,\mathrm{m^{-1} \, s^{-1}})$ ,<sup>[24]</sup>  $k_{3b}$  is roughly  $10^9 \,\mathrm{m^{-1} \, s^{-1}}$  in apolar solvents.

In conclusion, the present work provides new insights into the reactivity of hydroperoxyl radicals with a phenolic antioxidant of biological relevance. Lipid peroxidation in membranes is triggered by the fraction of HOO' able to penetrate the bilayer.<sup>[6,8c,25a]</sup> In our model system, the antioxidant action, i.e., HOO' trapping by an  $\alpha$ -tocopherol analogue is strongly enhanced by H-atom abstraction from HOO' by TO' radicals, a process resulting in the regeneration of TOH. This additional process can be biologically important, since  $\alpha\text{-tocopheroxyl}$  radicals formed during the antioxidant action of vitamin E are present at the water-lipid boundary region,<sup>[25]</sup> which can be easily accessed by HOO' (and to a different extent by O2'-, which is also able to regenerate the  $\alpha$ -tocopheroxyl radical).<sup>8c</sup> The strong kinetic solvent effect on the  $k_{3b}/k_{3a}$ , however, suggests that in H-bond-accepting solvents this reaction is not so efficient to dominate over the addition of HOO' to  $\alpha$ -tocopheroxyl radicals, as predicted by the conventional mechanism of the antioxidant action of  $\alpha$ -tocopherol.<sup>[8c]</sup>

Lastly, the kinetic solvent effect observed for the H-atom transfer from TOH to HOO' is much stronger than for the TOH/ ROO' pair, because of an H-bond formation between HOO' and H-bond-accepting solvents.

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# COMMUNICATION

#### Reactive Oxygen Species

J. Cedrowski, G. Litwinienko,\* A. Baschieri, R. Amorati\*

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Hydroperoxyl Radicals (HOO'): Vitamin E Regeneration and H-Bond Effects on the Hydrogen Atom Transfer



**Role reversal**: Hydroperoxyl radicals (HOO') are able to recycle an  $\alpha$ -tocopherol analogue, increasing the inhibition period up to 10 times, and exhibit a strong kinetic solvent effect arising from noncovalent interactions between HOO' and H-bond-accepting solvents.