Radical Reactions

DOI: 10.1002/anie.200903360

Unexpected Acid Catalysis in Reactions of Peroxyl Radicals with Phenols**

Luca Valgimigli, Riccardo Amorati, Silvia Petrucci, Gian Franco Pedulli, Di Hu, Jason J. Hanthorn, and Derek A. Pratt**

The formal transfer of a hydrogen atom from a phenol to a peroxyl radical [Eq. (1)] is a reaction widely recognized for its central role in the radical-trapping antioxidant activity of phenols, such as α-tocopherol (**1**),[1] and as a model for formal hydrogen-atom-transfer processes involving tyrosine (and tyrosyl radicals) in enzymatic reactions (e.g. prostaglandin and DNA biosynthesis).[2] The past ten years have brought a wealth of contributions that greatly enhance our understanding of this reaction, including the realization that it probably occurs by a concerted proton-coupled electron transfer (PCET) mechanism,[3] and that have clarified the basis for the long-observed structure–reactivity relationships,[4] whereby electron-rich phenols react fastest because of weaker O–H bonds.

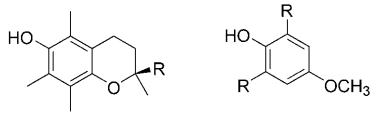
$$\mathrm{ArO\text{-}H} + {}^{\bullet}\mathrm{OOR} \rightarrow \mathrm{ArO}^{\bullet} + \mathrm{H\text{-}OOR} \qquad (1)$$

The importance of the radical-trapping chemistry of phenols in so many different physical contexts—be it in biological tissues or industrial and commercial materials—underscores the need for a firm grasp of medium effects on the kinetics of these formal hydrogen-atom-transfer reactions. Ingold and co-workers have clearly demonstrated the importance of hydrogen-bonding interactions between the phenol and solvent (or other hydrogen-bond acceptors in the medium) in retarding formal hydrogen-atom transfer from phenols to radicals.[5,6] This effect can be quantified by Equation (2), which relates the rate constant for the reaction of a phenol with a radical Y$^{\bullet}$ in any solvent ($k^{S}_{(\mathrm{ArOH;Y^{\bullet}})}$) to the rate constant in a non-hydrogen-bond-accepting solvent ($k^{0}_{(\mathrm{ArOH;Y^{\bullet}})}$) and the product of the hydrogen-bond-donating ability of the phenol and the hydrogen-bond-accepting ability of the medium, which are given by the Abraham parameters ${\alpha_{\mathrm{H}}}^2$ and ${\beta_{\mathrm{H}}}^2$, respectively.

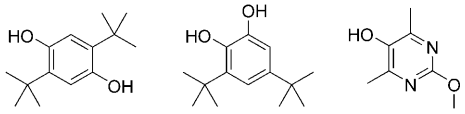
$$\log k^{S}_{(\mathrm{ArOH;Y^{\bullet}})} = \log k^{0}_{(\mathrm{ArOH;Y^{\bullet}})} - 8.3\,{\alpha_{\mathrm{H}}}^2\,{\beta_{\mathrm{H}}}^2 \qquad (2)$$

This relationship accounts for the kinetic solvent effects observed for a variety of phenol–radical couples;[7] the well-documented exception is those observed for the reactions of acidic phenols with electrophilic radicals in ionizing solvents (i.e. alcohols),[8] in which case the kinetics may be complicated by the contribution of a stepwise mechanism involving first proton transfer from the phenol to the solvent and then electron transfer from the phenoxide anion to the radical. Recently, in an attempt to minimize the contribution of this alternative mechanism in some of our own kinetic investigations of phenol–peroxyl reactions, we came upon a hitherto unknown aspect of phenol–peroxyl radical reactions: their dramatic acceleration with added acid. Herein we report our observations and discuss mechanistic interpretations and implications of this new and significant aspect of peroxyl-radical reactivity.

The rate constants for the reactions of peroxyl radicals with the five well-studied phenols **2**–**6**, which typify the



1 (R=$C_{16}H_{33}$) **3** (R = *t*Bu)
2 (R=CH_3) **4** (R = H)



5 **6** **7**

structural diversity encountered in the most common phenolic antioxidants, were determined in CH_3CN as a function of added acid. The reactions were monitored by the well-established methodology based on the inhibited autooxidation of styrene, whereby the rate constant (k_1) is related to the slope of the inhibited part of the oxygen-consumption trace.[9] A representative series of plots of the rate of oxygen consumption as a function of added acid is shown in Figure 1 for pentamethylchromanol (**2**), a model for the chemically active "head group" of α-tocopherol (**1**) in which the phytyl-derived hydrocarbon substituent at the 2-position is truncated. A dramatic rate acceleration is seen when the trace obtained without acid (dashed line) is compared to that obtained in the presence of AcOH (88 mM; solid line).

[*] Dr. L. Valgimigli, Dr. R. Amorati, Dr. S. Petrucci, Prof. Dr. G. F. Pedulli
Department of Organic Chemistry "A. Mangini"
University of Bologna
via San Giacomo 11, 40126 Bologna (Italy)
E-mail: luca.valgimigli@unibo.it
D. Hu, J. J. Hanthorn, Prof. Dr. D. A. Pratt
Department of Chemistry, Queen's University
90 Bader Lane, Kingston, ON K7L3N6 (Canada)
E-mail: pratt@chem.queensu.ca

[**] Grants from the University of Bologna, MIUR (Rome), NSERC Canada, Ontario MRI, and the Canada Research Chairs program are gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200903360.

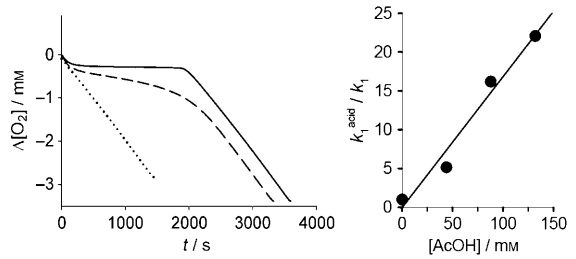


Figure 1. Left: oxygen consumption at 303 K during the azobisisobutyronitrile-initiated autooxidation of styrene (4.3 M) in "wet" CH_3CN (dotted line), and when the reaction is inhibited by pentamethylchromanol (**2**; 1.25 μM) in the absence (dashed line) or presence (solid line) of AcOH (88 mM); right: dependence of k_1 on the concentration of the acid.

Whereas the autooxidation of styrene in neat CH_3CN is only retarded by **2**, the addition of AcOH (88 mM) results in a fully inhibited autoxidation up to a reaction time of approximately 2000 s. This effect corresponds to a more than 16-fold increase in the k_1 value, from 6.8×10^5 to $1.1\times10^7\,M^{-1}s^{-1}$. This result is particularly striking when you consider that the rate constant determined for the reaction of **1** with peroxyl radicals by flash photolysis in neat AcOH ($k_1=8.8\times10^5\,M^{-1}s^{-1}$) is only roughly twice as large as that measured in CH_3CN ($k_1=3.8\times10^5\,M^{-1}s^{-1}$).[10]

The rate constants determined for **2**–**6** as a function of added AcOH are summarized in Table 1 (see the Supporting Information for all data). The substantial rate accelerations observed were proportional to the concentration of the acid and not to the strength of the acid: AcOH produced the largest effect for the series of acids surveyed (which also included HCl, *p*-toluenesulfonic acid, and trichloroacetic acid; see the Supporting Information for further details). No acceleration was observed in the apolar solvent chlorobenzene. For reproducible results, the addition of 1% water to rigorously dried acetonitrile was necessary. The addition of less water resulted in lower rate accelerations, whereas no further improvement was observed when water was added in larger amounts. Water itself (in the absence of acids) did not affect the rate of reaction.

Table 1: Rate constants for the reactions of phenols **2**–**6** and pyrimidinol **7** with peroxyl radicals, as determined at 303 K from inhibited autooxidation reactions of styrene in CH_3CN containing 1% H_2O, and the relative rate constants as a function of added AcOH.[a] Some relevant properties of **2**–**7** are included for comparison.

	k_1 [$M^{-1}s^{-1}$]	$\frac{k_1^{acid}/k_1}{[acid]}$[b]	BDE[c] [kcal mol^{-1}]	E_{pa}[d] [V vs. NHE]	α_H^2[e]
2	$(6.8\pm0.6)\times10^5$	170	77.1[21]	+1.13[19]	0.37
3	$(2.2\pm0.2)\times10^4$	3.9	77.2[21]	+1.31[20]	0.18[f]
4	$(5.0\pm1.0)\times10^3$	110	81.7[21]	+1.50[g]	0.57
5	$(8.0\pm0.5)\times10^4$	81	79.7[h]	+1.26[20]	0.55[f]
6	$(2.0\pm0.4)\times10^4$	1200	78.2[22]	+1.45[23]	0.69
7	$(7.9\pm5.2)\times10^2$	740	81.4[24]	+1.58[23]	0.64[f]

[a] Errors correspond to ±2 standard deviations. [b] Concentration of the acid in M. [c] Experimental O–H bond-dissociation energies in benzene at 298 K downscaled by 1.1 kcal mol^{-1} on the basis of the revised value for phenol.[25] [d] Experimental E_{pa} (anodic peak potential) in CH_3CN at 298 K. NHE = normal hydrogen electrode. [e] α_H^2 = Abraham hydrogen-bond-donor parameter.[26] [f] Estimated from kinetic measurements in different solvents and Equation (2). [g] The value from Ref. [27] was adjusted since the values reported therein are larger by approximately 0.2V than those from Refs. [23] and [19] for common compounds. [h] Value for 2,5-di-*tert*-amylhydroquinone.[22]

Some structure–activity data can be extracted from the data in Table 1, which lists the relative rate constants alongside some common thermodynamic properties relevant to phenolic-hydrogen-atom-transfer activity. At first glance, it is clear that the extent of acid catalysis is not simply related to the properties which normally influence the reactivity of phenols with peroxyl radicals, that is, in particular, the O–H BDE and/or the oxidation potential (E_{ox}) of the phenol. Instead, the dependence of the rate constant on the concentration of AcOH roughly parallels the hydrogen-bond acidity of the phenols, as quantified by the Abraham α_H^2 parameter.[26] This result suggests that the mechanism of the reaction of peroxyl radicals with phenols is different in the presence of acids from the mechanism in the absence of acids, as the acidity of the phenolic O–H group generally hampers the reaction (see above). To investigate this hypothesis further, we examined the effect of added AcOH on the autooxidation of styrene (again, in CH_3CN containing 1% H_2O) in the presence of the pyrimidinol **7**, a highly acidic phenol-like antioxidant with a relatively high oxidation potential and O–H BDE,[24] as the inhibitor in place of phenols **2**–**6**. Owing to the extent of H bonding to the solvent, the presence of **7** led to almost no inhibition of autooxidation under our experimental conditions in the absence of an acid; however, the addition of AcOH led to a dramatic increase in the k_1 value in a dose-dependent fashion. It was possible to increase the k_1 value by almost three orders of magnitude in this way (see the Supporting Information for further details).

To obtain direct kinetic evidence for the acid-accelerated reactions of peroxyl radicals with phenols, we turned to EPR spectroscopy. Although EPR is unsuitable for monitoring these reactions at room temperature, Fukuzumi et al. showed that the kinetics of reactions of cumylperoxyl radicals with substituted dimethylaniline derivatives and phenols can be studied in propionitrile at 193 K.[27,11] Through a slightly modified procedure, we were able to measure the k_1 values directly for the reactions of cumylperoxyl radicals with phenols **2**, **4**, and **6** by monitoring the signal decay of the cumylperoxyl radical formed upon photolysis of a mixture of cumene (2 M) and di-*tert*-butylperoxide (2 M) in oxygenated propionitrile in the presence of the phenols between 193–213 K. In the absence of phenols, the acid did not affect the lifetime of the cumylperoxyl radicals, which decayed with clean bimolecular kinetics with an apparent self-termination rate coefficient, $2k_t$, of $57\pm5\,M^{-1}s^{-1}$ at 193 K. However, when one of the phenols **2**, **4**, or **6** was present in excess, the decay was first-order, and the addition of an acid (HCl (100 mM), AcOH (150–300 mM), CCl_3CO_2H (150 mM)) accelerated the rate of decay in all cases (see the example in Figure 2). Interestingly, the relative rates were smaller at 193 K than those observed in the experiments on autooxidation kinetics at 303 K, and increased when the temperature was increased (see the Supporting Information). This observation suggests

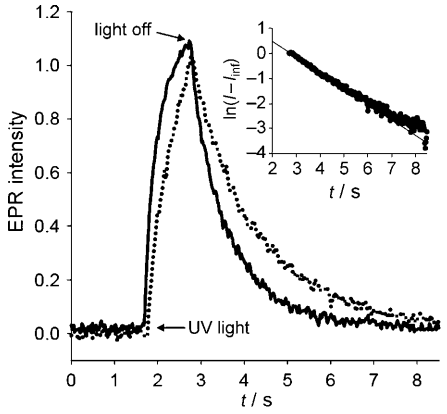
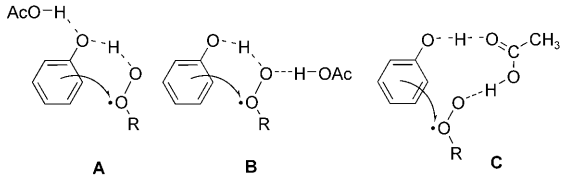


Figure 2. Evolution of the EPR signal at 193 K upon the irradiation of cumene (2 M) in propionitrile containing di-*tert*-butylperoxide (2 M) and 4-methoxyphenol (3.2 mM) in the absence of an acid (dotted line) or in the presence of 1% concentrated HCl (100 mM; solid line); inset: first-order plot of the signal decay in the presence of HCl.

that the acid catalysis involves an endothermic preequilibrium.

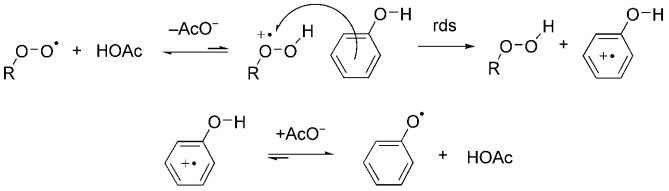
To provide some insight into the role of AcOH in the rate accelerations observed in reactions of phenols with peroxyl radicals, we calculated the activation energies for the transfer of the phenolic H atom from phenol to the methylperoxyl radical in the presence of formic acid and in its absence (see the Supporting Information for details). Three roles for the acid were envisioned: as a hydrogen-bond donor to the phenol (**A**), as a hydrogen-bond donor to the peroxyl radical (**B**), and as both a hydrogen-bond donor to the peroxyl radical and a hydrogen-bond acceptor to the phenol (**C**; Scheme 1).



Scheme 1. Low-energy transition states for the formal hydrogen-atom transfer from phenol to a peroxyl radical in the presence of AcOH.

The calculations revealed that the activation barrier for **B** was approximately 3 kcal mol^{-1} lower than that for the uncatalyzed reaction. Thus, an increase in the electrophilicity of the singly occupied molecular orbital of the peroxyl radical by hydrogen-bond donation by the acid can facilitate the reaction.

Although the hydrogen-bonding interaction between AcOH and the peroxyl radical (or the partial protonation of the radical) seems highly reasonable and is supported by the calculations, we wondered whether discrete protonation of the peroxyl radical (a process that is impossible to capture in the calculations) to render it an even better electrophile could also be a possibility. Such protonation would explain the need for a polar solvent (no acceleration was observed in chlorobenzene) and could also account for the endothermic preequilibrium suggested by the results of the low-temperature EPR study. Indeed, the rate of hydrogen-atom abstraction by aminium radicals ($R_2NH^{\bullet+}$),[12] a process key to radical chain propagation in the acid-catalyzed chlorination of hydrocarbons by chloramines,[13] is much faster than the rate of hydrogen-atom abstraction by aminyl radicals ($R_2N^{\bullet}$), as the protonated species $R_2NH^{\bullet+}$ are more electrophilic. Although the basicity of aminyl radicals ($pK_a \approx 7$)[12] is undoubtedly greater than that of peroxyl radicals (unknown),[14] the same rate enhancement upon protonation of peroxyl radicals can be envisioned. These considerations suggest another mechanistic possibility, whereby a rapid equilibrium between the acid and the peroxyl radical precedes rate-determining electron transfer from the phenol to the hydroperoxide radical cation.[15] This mechanism (Scheme 2)[16] would operate best with weak organic acids



Scheme 2. Proposed mechanism of the acid-catalyzed reaction of peroxyl radicals with phenols. rds = rate-determining step.

that show good solubility in CH_3CN and are not strong enough to protonate the phenol and impair the electron-transfer step. Hydrogen bonding between the phenol and CH_3CN (which dramatically slows the rate of reaction with peroxyl radicals in the absence of an acid, see above) may facilitate the reaction by stabilizing the phenolic radical cation formed in the putative rate-determining step.

The mechanism shown in Scheme 2 is supported by deuterium kinetic isotope effects (DKIEs) measured for inhibited styrene-autooxidation reactions of **2** and **6** with peroxyl radicals in CH_3CN (see the Supporting Information for details). In the absence of acids, we obtained k_H/k_D values of 6.4 ± 1.3 and 4.6 ± 1.0 for **2** and **6**, respectively. These values compare well to previous measurements with **2** ($k_H/k_D = 5.5$ in styrene) and other phenols (e.g. α-tocopherol, $k_H/k_D = 5.4$ in styrene). These primary DKIEs are consistent with a mechanism in which a hydrogen atom is transferred in the rate-determining step (as in a hydrogen-atom-transfer (HAT) or PCET mechanism). Interestingly, the k_H/k_D values for reactions of **2** and **6** with peroxyl radicals were *inverse* in the presence of added acetic acid (0.9 ± 0.3 and 0.6 ± 0.2, respectively): a clear indication of a change in mechanism. The values of k_H/k_D lower than unity are consistent with the mechanism in Scheme 2, in which a rapid equilibrium involving proton (deuteron) transfer precedes a slower electron-transfer step.[17]

The significance of our results is clear for applications involving antioxidants, be it in biological or industrial settings. The presence of small amounts of acid leads to a dramatic acceleration of the rate of reactions between phenols and chain-carrying peroxyl radicals and thus increases the efficacy

of these reactions. It is less clear whether nature has made use of this mechanism to accelerate the rate of formal hydrogen-atom-transfer reactions under enzyme catalysis or in other biological contexts. The significantly depressed pH value of the lysosome (ca. 4.8)[18] has long been thought to support the proteases that have evolved to function optimally at lower pH values to degrade superfluous proteins or pathogenic materials. The selective advantage has long been recognized to safeguard the cell from degradation by proteases should they not remain confined to the lysosome. Another selective advantage may be the more effective oxidizing power of the lysosome at acidic pH values: the oxidative chemistry important in the phagolysosomes of phagocytes responsible for the destruction of pathogens as part of the immune response is thus more facile.

Received: June 21, 2009
Revised: August 10, 2009
Published online: September 25, 2009

Keywords: antioxidants · EPR spectroscopy · hydrogen transfer · kinetics · proton-coupled electron transfer

[1] G. W. Burton, K. U. Ingold, *Acc. Chem. Res.* **1986**, *19*, 194.
[2] W. A. van der Donk, J. Stubbe, *Chem. Rev.* **1998**, *98*, 705.
[3] G. A. DiLabio, E. R. Johnson, *J. Am. Chem. Soc.* **2007**, *129*, 6199.
[4] D. A. Pratt, G. A. DiLabio, P. Mulder, K. U. Ingold, *Acc. Chem. Res.* **2004**, *37*, 334.
[5] D. W. Snelgrove, J. Lusztyk, J. T. Banks, P. Mulder, K. U. Ingold, *J. Am. Chem. Soc.* **2001**, *123*, 469.
[6] G. Litwinienko, K. U. Ingold, *Acc. Chem. Res.* **2007**, *40*, 222.
[7] For peroxyl radicals, see: M. Jha, D. A. Pratt, *Chem. Commun.* **2008**, 1252.
[8] G. Litwinienko, K. U. Ingold, *J. Org. Chem.* **2003**, *68*, 3433, and related references cited in Ref. [6].
[9] G. W. Burton, T. Doba, E. Gabe, L. Hughes, F. L. Lee, L. Prasad, K. U. Ingold, *J. Am. Chem. Soc.* **1985**, *107*, 7053.
[10] L. Valgimigli, J. T. Banks, J. Lusztyk, K. U. Ingold, *J. Org. Chem.* **1999**, *64*, 3381.
[11] S. Fukuzumi, K. Shimoosako, T. Suenobu, Y. Watanabe, *J Am Chem. Soc* **2003**, *125*, 9074.
[12] a) J. Spanswick, K. U. Ingold, *Can. J. Chem.* **1970**, *48*, 554; b) V. Malatesta, K. U. Ingold, *J. Am. Chem. Soc.* **1973**, *95*, 6400 – 6404.
[13] Y. L. Chow, W. C. Danen, S. F. Nelsen, D. H. Rosenblatt, *Chem. Rev.* **1978**, *78*, 243.
[14] On the basis of hydrogen-bonding interactions with $(CF_3)_2CHOH$ (V. Mugnaini, M. Lucarini, *Org. Lett.* **2007**, *9*, 2725), the basicity of peroxyl radicals is estimated to be higher than that of phenols.
[15] The change that would be expected in the EPR spectrum of the peroxyl radical upon protonation or hydrogen-bond donation by the added acid was not observed, presumably because of the unfavorable equilibrium.
[16] The small amounts of water needed may also be required to help disrupt acetic acid dimers, to afford more of the free acid to participate in the reaction.
[17] It has been suggested that the Lewis acid complexation of water or alcohols lowers their O–H BDE, which accounts for the observation that these compounds donate H atoms under such conditions (see, for example: D. A. Spiegel, K. B. Wiberg, L. N. Schacherer, M. R. Medeiros, J. L. Wood, *J. Am. Chem. Soc.* **2005**, *127*, 14204). Likewise, it is known that intramolecular hydrogen-bond donation to phenols lowers their O–H BDE, since the phenoxyl radical is a better hydrogen-bond acceptor than the phenol itself.[14] However, both the values of k_H/k_D and the lack of an observed increase in the rate acceleration with increasing strength of the added acid are inconsistent with this type of mechanism.
[18] S. Ohkuma, B. Poole, *Proc. Natl. Acad. Sci. USA* **1978**, *75*, 3327.
[19] L. L. Williams, R. D. Webster, *J. Am. Chem. Soc.* **2004**, *126*, 12441.
[20] R. Akasaka, R. Teshima, S. Kitajima, J. Momma, T. Inoue, Y. Kurokawa, H. Ikebuchi, J. Sawada, *Biochem. Pharmacol.* **1996**, *51*, 1513.
[21] M. Lucarini, P. Pedrielli, G. F. Pedulli, S. Cabiddu, C. Fattuoni, *J. Org. Chem.* **1996**, *61*, 9259.
[22] M. Lucarini, V. Mugnaini, G. F. Pedulli, *J. Org. Chem.* **2002**, *67*, 928.
[23] D. T. Sawyer, M. G. Gibian, M. M. Morrison, E. T. Seo, *J. Am. Chem. Soc.* **1978**, *100*, 627.
[24] L. Valgimigli, G. Brigati, G. F. Pedulli, G. A. DiLabio, M. Mastragostino, C. Arbizzani, D. A. Pratt, *Chem. Eur. J.* **2003**, *9*, 4997.
[25] P. Mulder, H.-G. Korth, D. A. Pratt, G. A. DiLabio, L. Valgimigli, G. F. Pedulli, K. U. Ingold, *J. Phys. Chem. A* **2005**, *109*, 2647.
[26] M. H. Abraham, P. L. Grellier, D. V. Prior, P. P. Duce, J. J. Morris, P. J. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1989**, 699.
[27] T. Osako, K. Ohkubo, M. Taki, Y. Tachi, S. Fukuzumi, S. Itoh, *J. Am. Chem. Soc.* **2003**, *125*, 11027.

