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Advances in Radical-Trapping Antioxidant Chemistry in the 21st Century: A Kinetics and Mechanisms Perspective

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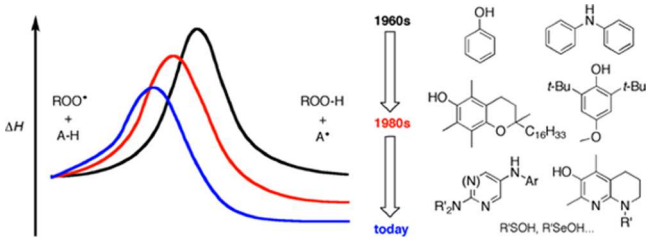

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1. INTRODUCTION

Oxidative degradation of organic materials in air generally involves a free radical chain, reactions 1−6 (see Scheme 1). The chain reaction begins with formation of an initiating radical, In$^{\bullet}$, by some thermal or photochemical process. If In$^{\bullet}$ is, or rapidly forms, a carbon-centered radical there will generally be a fast addition of molecular oxygen to give a chain-initiating peroxyl radical, InOO$^{\bullet}$. The overall rate of initiation is represented by R_i. There are two chain-propagating steps; reaction 2 is roughly diffusion controlled ($k_2 \approx 10^9$ M^{-1} s^{-1})[1] and usually gives the substrate-derived peroxyl radical, ROO•.[2] The next step is generally very slow (typical k_3 values range from <1 to ca. 100 M^{-1} s^{-1} at ambient temperatures).[6] Chains are terminated by radical/radical reactions with two chains being terminated per event, reactions 4−6.

Under normal atmospheric partial pressure of oxygen, the rate of reaction 3 is much lower than the rate of reaction 2;

Scheme 1. Radical Chain Mechanism of Hydrocarbon Autoxidation

Initiation

$$\longrightarrow \text{In}^{\bullet} \xrightarrow{O_2} \text{InOO}^{\bullet} \xrightarrow{RH} \text{InOOH} + \text{R}^{\bullet} \quad (1)$$

Propagation

$$\text{R}^{\bullet} + O_2 \xrightarrow{\text{fast}} \text{ROO}^{\bullet} \quad (2)$$

$$\text{ROO}^{\bullet} + \text{RH} \xrightarrow{\text{slow}} \text{ROOH} + \text{R}^{\bullet} \quad (3)$$

Termination

$$\text{R}^{\bullet} + \text{R}^{\bullet} \xrightarrow{\text{fast}} \quad (4)$$

$$\text{ROO}^{\bullet} + \text{R}^{\bullet} \xrightarrow{\text{fast}} \quad (5)$$

$$\text{ROO}^{\bullet} + \text{ROO}^{\bullet} \xrightarrow{\text{slow}} \quad (6)$$

} non-radical products

therefore, the steady-state concentration of ROO$^{\bullet}$ is very much greater than the steady-state concentration of R$^{\bullet}$. Reactions 4 and 5 are generally diffusion controlled, but nevertheless, termination commonly occurs solely via the much slower reaction 6 (k_6 is structure dependent ranging from 10^3 to 10^5

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M^{-1} s^{-1} for tertiary alkylperoxyls to 10^6 to 10^8 M^{-1} s^{-1} for secondary alkylperoxyls).[6] The initial rate of the overall reaction is given by

$$d[ROOH]/dt = -d[O_2]/dt = k_3[RH](R_i/2k_6)^{1/2} \quad (I)$$

Retarding oxidative degradation is of enormous economic importance for essentially all petroleum-derived materials such as engine lubricating oils, rubber, fuels, and plastics. For such substrates under normal usage conditions, the only practical approach to retarding degradation is addition to the substrate of "*antioxidants*" of sufficient activities and in sufficient concentrations to achieve the desired stability. Because of the commercial importance of antioxidants, research into the molecular mechanisms by which they exert their protective effects has long been a major theme of free radical chemistry. By the middle of the 20th century it was recognized that antioxidants should be divided into two main classes.[7]

(i) *Radical-Trapping Antioxidants* (RTAs), also known as *chain-breaking antioxidants*, capture chain-carrying radicals and thus break the oxidation chain.

(ii) *Preventive Antioxidants* reduce the rate at which *new* radical chains are started.

By the final quarter of the 20th century, the commercial importance of antioxidants was overshadowed by their putative role in human health, as the implication of radical-mediated oxidation in virtually all types of degenerative diseases, including cancer and aging, emerged. From then on, antioxidant chemistry was no longer simply a major theme of free radical chemistry but became a much larger, broader research area, counting pharmacologists, nutritional biochemists, biologists, and still others among its most active participants. Many believed that antioxidants would prove to be the "silver bullet" that medicine had been searching for and that the deleterious effects of radical-mediated oxidation believed to underlie degenerative disease development could be prevented or even treated. Even a casual survey of the scientific literature reveals the popularity of these ideas, and given the simple, dichotomous concept of the balance between antioxidants and oxidants being at the center of degenerative disease development, the popular press was quick to hop on board the bandwagon, fuelling the search for plant-derived vitamins or other phytochemicals that might prove to be "the one". More sober thoughts prevailed toward the end of the 1990s, with the realization that things were, in fact, far more complicated. Regardless, a compelling case can still be made for a role for radical-trapping antioxidants in the maintenance of good health and longevity. However, this case will not be presented here as it lies beyond the chemical focus and temporal scope of the present review. Readers are directed to Halliwell and Gutteridge's *Free Radicals in Biology and Medicine*, already in its fourth edition in 2007,[8] for a comprehensive account of the state of the art.

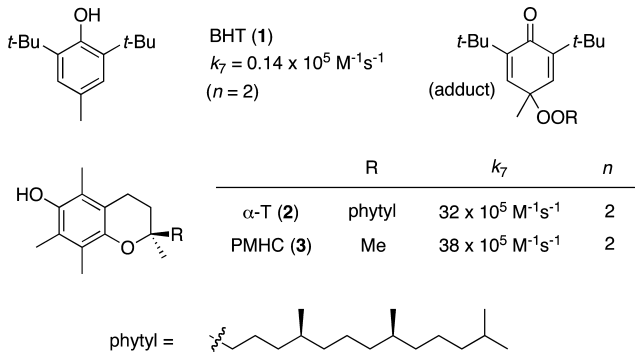
Significant breakthroughs occur even in such an intellectually stimulating and "well-ploughed" scientific field as antioxidant chemistry. This is evident in a recent comprehensive review[9] and in two other excellent recent reviews of more limited scope, one dealing with phenolic RTAs[10] and the other with nonphenolic RTAs.[11] All three of these reviews touch briefly on some of the topics of the present review, which has the more limited objective of describing the numerous important advances in RTA chemistry that have been made since the turn of the current century. In each of these areas, the state of knowledge prior to the seminal breakthrough will be briefly presented, followed by a more detailed discussion of the specific advance and where it may be leading. Brief, critical appraisals of various erroneous "short cuts" to discovering "new/improved" RTAs by theory or experiment will be included where appropriate without "finger pointing", i.e., without references both to avoid giving embarrassment and because the number of such claims is quite overwhelming.

2. PEROXYL RADICAL TRAPPING BY PHENOLS AND CLOSELY RELATED COMPOUNDS

2.1. Historical Background

Our understanding of RTAs has come largely from work using phenols, both synthetic, e.g., 2,6-di-*tert*-butyl-4-methylphenol (BHT, **1**),[12] and natural, e.g., 2*R*, 4′*R*, 8′*R*-α-tocopherol (α-T, **2**),[13,14] and α-T's truncated analogue, 2,2,5,7,8-pentamethylchromanol (PMC, **3**),[13,14] see Chart 1. BHT (**1** and derivatives thereof) is the major RTA used commercially, while α-T (**2**) is not only the best in vitro RTA of the four tocopherols that together constitute Vitamin E but also the most biologically active form of Vitamin E.[13] These three phenols (and virtually all other phenols) each capture two peroxyl radicals, that is, the stoichiometric factor for peroxyl radical capture, *n*, for most phenols is 2.0. The first ROO• "captures" a phenolic H-atom, reaction 7, see Scheme 2 (rate constants, k_7, are from ref 14). The phenoxyl radical so formed should be too unreactive to abstract an H-atom from RH or ROOH. If such abstractions should prevail (reactions 9 and 10) the phenol would be an ineffective RTA and simply function as a chain-transfer agent

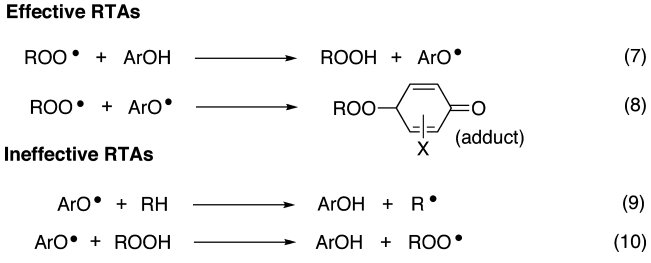
Chart 1[a]



	R	k_7	n
α-T (**2**)	phytyl	32 x 10^5 M^{-1}s^{-1}	2
PMHC (**3**)	Me	38 x 10^5 M^{-1}s^{-1}	2

[a]Note: Rate constants for ROO• trapping were generally determined at 30, 37, or 65 °C. Because the activation enthalpies for all useful RTAs are small, the temperature at which particular inhibition rate constants were measured has not always been included in this review.

Scheme 2. Key Reactions in the Inhibition of Hydrocarbon Autoxidation by Phenolic Radical-Trapping Antioxidants



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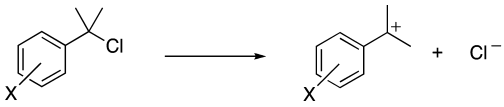
continuing the chain but at a reduced rate. (A full kinetic analysis of RTAs that are ineffective because of chain transfer has been presented.[15]) For phenols that are effective RTAs (and therefore practically useful) the phenoxyl radical "sits around" until it encounters a second peroxyl radical with which it couples very rapidly, reaction 8. The initial rate of an inhibited autoxidation for effective RTAs is given in eq II

$$d[ROOH]/dt = -d[O_2]/dt = k_3[RH]/2k_7[ArOH] \quad (II)$$

As early as 1963 it was discovered[16] that inhibition of the autoxidation of styrene at 65 °C by meta- and para-substituted phenols, X-C_6H_4OH, gave an excellent Hammett correlation using Brown and Okamoto's[17] electrophilic substituent constants, $\sigma^+(X)$, eq III

$$\log(k_7^{X-C6H4OH}/k_7^{PhOH}) = \rho\sigma^+ \quad (III)$$

These σ^+ substituent constants are based on the relative rates of solvolysis of cumyl chlorides in 90% acetone/water at 25 °C.[17]

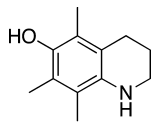


(11)

The RTA activities of the phenols were decreased by electron-withdrawing ring substituents and increased by electron-donating substituents. These effects were substantial ($\rho^+ = -1.58$) with k_7 increasing by a factor of 3.2 and 16.4, respectively, upon increasing the electron-donating power of the para substituent from H ($\sigma_p^+ = 0$), to CH_3 ($\sigma_p^+ = -0.31$), and to OCH_3 ($\sigma_p^+ = -0.78$). It was later shown that log k_7 correlated with the XC_6H_4O-H bond dissociation enthalpies, BDEs.[9,18] This correlation with σ^+ arises because the phenoxyl radical center, $O^\bullet$, is (like the C^+Me_2 group, eq 11) strongly electron-withdrawing.[18,19]

Dialkylamino groups are very much stronger electron donors ($\sigma_p^+ = -1.7$) than alkoxy groups but cannot be used to make even better phenolic RTAs.[20] This is because the presence of two strong electron-donor groups in aminophenols (R_2N and OH) lowers their ionization potentials to the point that there is a direct electron transfer to dioxygen, reaction 12. For example, the aminophenol **4** was rapidly consumed when a solution was exposed to air at room temperature.[14]

$$O_2 + R_2NC_6H_4OH \rightarrow O_2^{\bullet-} + (R_2NC_6H_4OH)^{\bullet+}$$
$$\rightarrow R_2NC_6H_4O^\bullet + H^+ \quad (12)$$



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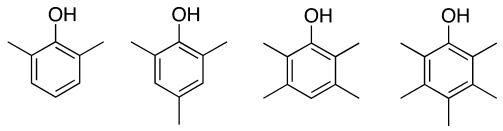
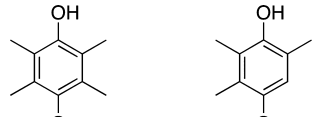
Another approach to increasing the RTA activities of phenols without hitting the "brick wall" of electron transfer to dioxygen was multiple ring methylation.[23] The relative rate data[16] in Chart 2 suggested that the most active phenolic RTA would be 4-methoxy-2,3,5,6-tetramethylphenol, **5**, the substitution pattern which mirrors that of the excellent phenolic RTAs, **2** and **3**, see Chart 1. Surprisingly, the k_7 value for **5** was later found[14] to be only about 10% of the k_7 value for **2** or **3**, but removal of one of its (normally activating) *meta*-methyl groups to form **6** increased k_7 by a factor of 3.3 (Chart 3).

Chart 2

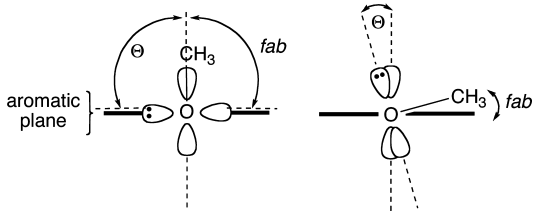


k_7/k_7(PhOH)	3.1	9.6	4.6	13.2

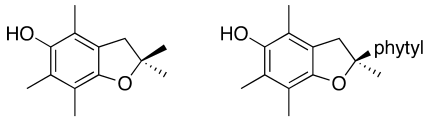
Chart 3



	5	**6**
$10^{-5}k_7$ / $M^{-1}s^{-1}$	3.9	13
k_7/k_7(PhOH)	48	160
Θ (=*fab*)	89°	8°



The stereoelectronic explanation for these results relates to the extent of stabilization of the phenoxyl radical by overlap between the lone pairs on the alkoxy group's O-atom and the aromatic π-electron system. This stabilizing overlap reduces the O−H BDE and hence increases the value of k_7. Overlap is maximized when the dihedral angle between the O−CH_3 bond (O−C_2 bond for **2**, **3**, etc.) and the aromatic ring, fab (which should equal Θ), (see Chart 3), is 0° and minimized when this dihedral angle is 90°. These dihedral angles are readily determined by X-ray crystallography,[14] see Chart 3 where, for clarity, the two sp^3 lone pairs on the methoxyl's O-atom have been rehybridized to an sp^2-type lone pair (not shown) and a 2p-type lone pair (shown). The heterocyclic ring in **3** (and presumably in noncrystalline **2**) has a half-chair conformation which precludes really good orbital overlap (Θ ≈ 17°). It was hypothesized, and readily proved, that reduction of the 6-membered heterocyclic ring to a 5-membered ring would decrease Θ to near 0°, increasing orbital overlap and hence k_7. The resultant 2,3-dihydro-4,6,7-trimethyl-5-hydroxybenzofuran, **7**, does not undergo electron transfer with O_2, and with a k_7 value of 57×10^5 M^{-1} s^{-1}, it would appear to be the most active of all *simple* phenolic RTAs. (Amusingly, addition of the phytyl "tail" present in α-tocopherol, **2**, gave a compound, **8**, which, in one bioassay at least, had nearly twice the Vitamin E activity of **2**.)[24]



7 **8**

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2.2. What Properties Would a "Perfect" H-Atom Donor Radical-Trapping Antioxidant (RTA) Require?

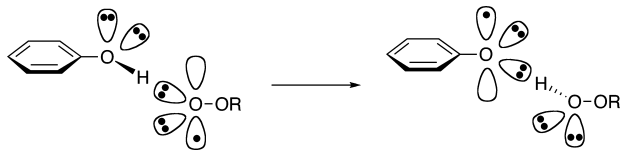
The obvious requirements are as follows. (i) The *"holy grail"* for any kinetically "*perfect*" RTA would be a compound that reacted with the first peroxyl radical it encountered, i.e., that reacted at the diffusion-controlled limit. Note that the value of k_7 measured for the "optimized" "simple" phenolic RTA, **7**, is only ca. 1% of this value! (ii) If the "perfect" RTA is to be an H-atom donor, AH, the derived A$^\bullet$ must not continue the chain (see reactions 9 and 10). It should either trap a second ROO$^\bullet$ (see reaction 8), i.e., n = 2.0, or, better yet, enter into some "catalytic cycle" with the eventual capture of many radicals, i.e., $n \gg 2.0$. (iii) To achieve a fast H-atom transfer to ROO$^\bullet$, the bond dissociation enthalpy (BDE) of A−H has to be significantly less than the ROO−H BDE (~88 kcal/mol). Although this BDE requirement is a necessary condition for a fast ROO$^\bullet$ + AH reaction, it is not a sufficient condition.

In connection to iii, it should be noted that there have been many computational reports that have claimed to have uncovered some new type/class of RTAs in the mistaken belief that the rates of ROO$^\bullet$ + AH reactions depend solely on the A−H BDE. *It has long been known that this is not the case.* Hydrogen abstraction by ROO$^\bullet$ from XHs of essentially equal BDEs is very much faster for X = O (or N) than for X = C. For example, the $PhCH_2$−H and PhO$^\bullet$H BDEs are almost identical,[18,25,26] but the 30 °C rate constants for H-atom abstraction by ROO$^\bullet$ favor abstraction from the O−H by 4 orders of magnitude, viz., $k/M^{-1}\ s^{-1} \approx 3000$ for phenol[16] but only ~0.24 (0.08 after statistical correction!) for toluene[6] (and ~20 000 for diphenylamine,[27] for which the N−H BDE is 2.5 kcal/mol weaker than the PhO−H BDE). (Note, in connection to *i*, some computational reports do actually calculate rate constants to predict RTA activity based on transition state theory, but they generally employ either hydroxyl or hydroperoxyl radicals.) These radicals are generally not appropriate. Essentially all organic compounds react with hydroxyl radicals at rates of, or approaching, diffusion, making it highly unlikely that such reactions underlie their (potential) antioxidant activity.[28] Hydroperoxyl radicals are poor models: HOO—H BDE > ROO−H BDE, $E°$ (HOO$^\bullet$) > $E°$ (ROO$^\bullet$), and they possess an acidic O−H bond which can serve as a H-bond donor to H-bond-accepting sites on the antioxidant under study. Since most computations are carried out in the gas phase, this H-bonding interaction can be very strong and will render comparison to reality questionable.

Several explanations for the rate acceleration of H-atom transfers between two heteroatoms have been advanced. To the present authors, it seems probable that this acceleration arises from the combination of two interlinked factors: (a) a difference in the mechanism of H-atom abstraction by ROO$^\bullet$ from CH vs OH and NH groups and (b) the presence or absence of an H-bonded complex between the substrate and the radical. It is impossible to say which (if either) of these two factors is the more important.[29] Both are briefly described below.

2.2.1. Differences in Mechanism. Mayer et al.[33] made the insightful suggestion that H-atom transfers between heteroatoms can occur by a distinctly different mechanism to H-atom transfers between carbon atoms (or between a carbon atom and a heteroatom). The heteroatom/heteroatom mechanism was christened proton-coupled electron transfer (PCET). It involves the transfer of a proton from the substrate to a lone pair on the atom bearing the unpaired electron together with simultaneous transfer of an electron from a lone pair on the substrate to the orbital occupied by the unpaired electron, i.e., the SOMO. The proton is transferred within the plane of the local molecular framework, and the electron is transferred between orbitals that are generally, but not always,[34] perpendicular to this plane. A "classic" PCET mechanism is illustrated for the reaction of phenol with a peroxyl radical in Chart 4. Such mechanisms are only possible when the H-atom

Chart 4



is transferred between two heteroatoms since only these possess the requisite lone pairs. (An H-atom transfer that involves only one, or no, heteroatom must be a hydrogen-atom transfer (HAT), with the proton moving along with one of its bonding electrons toward the SOMO of the radical.) It is important to note in Chart 4 that the electron is transferred from a lone pair in an orbital roughly orthogonal to the aromatic ring plane. This means that the "new" unpaired electron develops in an orbital that is also orthogonal to the plane of the aromatic ring, that is, the "new" unpaired electron is formed with maximum 2p−π orbital overlap, corresponding to maximum PhO$^\bullet$ resonance stabilization.

For clarity only, Chart 4 shows an anti arrangement of the reactants (PhOH and ROO$^\bullet$) and products (PhO$^\bullet$ and ROOH). However, computations indicate that a syn arrangement of substrate and radical is preferred in the transition states of most, if not all, YO$^\bullet$ + XOH reactions. In the syn transition state (TS), the Y and X moieties are positioned on the same side of the oxygen atoms between which the H-atom is formally being transferred due to the overlap between orbitals centered on X and Y[34−40] (e.g., for the ROO$^\bullet$ + PhOH reaction, between the 2p lone pairs on the inner O-atom of ROO$^\bullet$ and the π electrons of the aromatic ring).[34−36] This additional overlap stabilizes the transition state. This arrangement of the reactants necessarily introduces HAT character into the TS. Indeed, in the limit of a syn TS in which the ROO$^\bullet$ is centered directly "above" the phenol, the O−H bond in the phenol will be perpendicular to the aromatic ring and the SOMO of ROO$^\bullet$ will be perpendicular to the plane defined by the C−O−O$^\bullet$ moiety. This is, of course, a HAT TS which would seem to be disfavored relative to an anti PCET TS, that is, the prereaction HB complex (see below) will be weaker because a phenol with its O−H bond perpendicular to its ring will be a weaker HBD than a phenol with its O−H in plane (cf. acidities and HBD activities of alcohols vs phenols) and because the HBA ability of an orbital containing a single electron will be less than that of a lone pair orbital on the same atom. In reality, the TSs for ROO$^\bullet$ + ArOH reactions are probably some combination of anti PCET-type and syn HAT-type processes. It should be mentioned that while PCET requires H-atom exchange between heteroatoms, syn transition states have no such requirement. In fact, they are preferred for reactions involving only one heteroatom (ROO$^\bullet$ + H−CH_2CH=CH_2)[41] or no heteroatoms at all ($PhCH_2^\bullet$ + $PhCH_3$).[33] PCET has been reviewed.[42,43]

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2.2.2. Formation of a Prereaction, Hydrogen-Bonded Complex. These are intrinsic whenever the labile H-atom is acidic and allows the substrate to serve as a HBD to an attacking HBA radical. For RTAs, the HB complex will be formed between the leading O-atom of the peroxyl radical and the OH or NH group of the RTA (see, e.g., Chart 4). Formation of a prereaction HB complex will accelerate the RTA reaction by causing the two heteroatoms (O$^{\bullet}$ and O or N) to approach each other more closely than in the absence of a HB, an effect that narrows and further reduces the barrier to reaction. An attempt has been made to capture the energy profiles of thermoneutral H-atom abstractions without and with a HB prereaction complex in Figure 1. The barrier height from

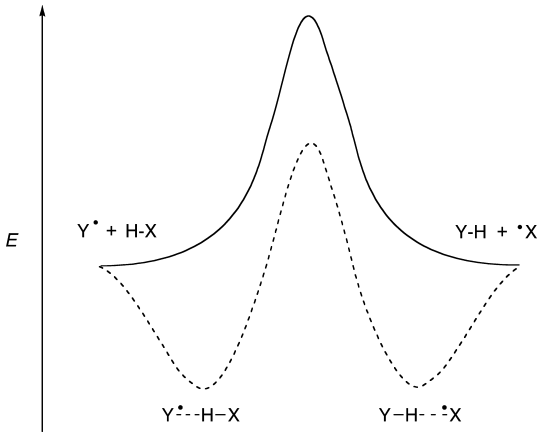


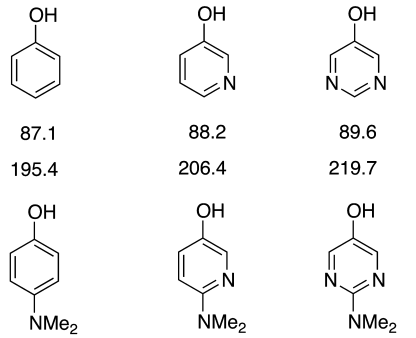
Figure 1. Potential energy profiles for barriers of equal height for thermoneutral hydrogen/proton transfers with (dashed line) and without (solid line) a HB prereaction complex.

the HB complex to the transition state has been made equal to that for the no-complex process. However, from the HB-forming reactants' viewpoint, the barrier has become lower and narrower (which will encourage proton transfer by quantum mechanical tunneling). It should be noted that if the HB complex was twice as strong as that shown in Figure 1, the free reactants would encounter no barrier to reaction, and therefore, they would be *kinetically perfect RTAs*! The RTA activities of simple phenols might therefore be expected to increase as the HB donor activities of the phenols are increased by adding electron-withdrawing (EW) substituents to the ring. Unfortunately, EW substituents also increase the O−H BDE and thus reduce k_7, i.e., the potential benefits from substituent-induced stronger ArOH---$^{\bullet}$OOR HBs in phenols are negated by BDE changes.

2.3. Pushing to the Limit: Pyridinols and Pyrimidinols

To approach the diffusion-controlled limit for k_7 for a phenolic RTA requires that the O−H BDE be reduced well below that of **2** and **3** (77 kcal/mol), *without* lowering the IP to the point where there is a direct reaction with O_2. This was one of the major challenges facing free radical chemistry toward the end of the 20th century. The seemingly intractable problem that had to be overcome was that *both* phenolic O−H BDEs decrease (desired) and phenolic IPs decrease (undesired) as the energy of the HOMO is increased by adding stronger ED groups to the aromatic ring. The solution to this dilemma, first reported in 2001,[44] was enabled by computation; in particular, DFT methods that reliably reproduced experimental BDEs[45] and ionization potentials.[46,47] Such calculations indicated that substitution of N for C at the 3 position of phenol would increase the IP by over 10 kcal/mol but would increase the O−H BDE by only 1.1 kcal/mol. In addition, introducing a second N at the 5 position would further increase the IP by almost 15 kcal/mol but only increase the O−H BDE by another 1.4 kcal/mol, see Chart 5.[44] Furthermore, these calculations indicated

Chart 5. Calculated Gas-Phase O−H BDEs at 298 K and Calculated Adiabatic Ionization Potentials at 0 K, Both in kcal/mol[44a]



O-H BDE	87.1	88.2	89.6
IP	195.4	206.4	219.7
O-H BDE	77.0 (-10.1)	77.0 (-11.2)	78.3 (-11.3)
IP	157.7 (-37.7)	164.6 (-41.8)	174.6 (-45.1)

[a]Substituent effects, relative to the unsubstituted parent compound, are in parentheses.

that substituents para to the OH group produced very similar changes in O−H BDEs and IPs in phenols, pyridinols, and pyrimidinols, see, e.g., the effects of the dimethylamino group (Chart 5).[44]

Subsequent development of these heterocyclic phenol analogs, pyridinols[49] and pyrimidinols,[50] followed, enabled first by a collaboration between one of us and the Valgimigli group at the University of Bologna and later the Porter group at Vanderbilt University. The more electron-poor heteroaryl rings enabled substitution with not only dialkylamino groups (the most powerful of all electron-donating substituents excepting a negatively charged group such as O^{-}) para to the OH group but also containing two electron-donating methyl groups in the ortho positions for good measure, see Chart 6. Thanks to their high IPs, these compounds were found to be sufficiently robust that, in contrast to dialkylaminophenols, they could be prepared and purified without exclusion of air. (Air exclusion is also advisible when purifying α-tocopherol, **2**.) Moreover, thanks to their low O−H BDEs, these compounds were, as predicted, outstanding RTAs with the pyrimidinol, **11**, having a k_7 value twice that of **2** and the pyridinol, **10**, having a k_7 value five times greater than **2**, see Chart 6. The k_7 value of **10** was greatly enhanced (taking a leaf from the earlier work on phenolic RTAs) by locking the lone pair on the nitrogen of the substituent in a position more or less orthogonal to the aromatic plane via a fused ring, i.e., compounds **12** and **13** in Chart 6. These last two compounds were found to be 28 and 88 times, respectively, more active peroxyl radical traps than **2**, *and their k_7 values approach the diffusion-controlled limit.*

Unfortunately, **13** does have one serious shortcoming that would seem to preclude its hoped use as an RTA. This shortcoming was foretold by theory, which indicated that its IP was just as low as that for **9** (viz. 152.3 kcal/mol, see Chart 6) implying that **13** (like **9**) would react directly and rapidly with

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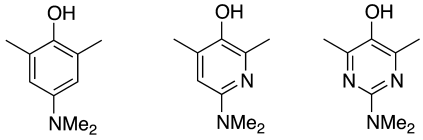
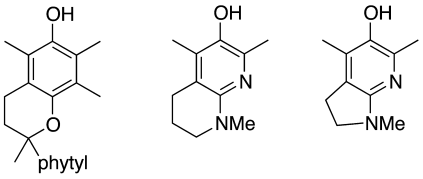
Chart 6. Calculated Gas-Phase (followed in parentheses by available experimental) O−H BDEs at 298 K[48] and Calculated Adiabatic Ionization Potential at 0 K[48] (both in kcal/mol) and Rate Constants, k_7, for Reaction with ROO• at 30 °C[48] (50 °C for 11)[44]



	9	**10**	**11**
O-H BDE	72.3	73.5 (77.0)	74.1 (78.2)
IP	152.3	157.7	167.0
$10^{-5}k_7$ / $M^{-1}s^{-1}$	---	160	86
n	---	2	2



	2	**12**	**13**
O-H BDE	74.8 (78.3)	73.3 (76.3)	72.4 (75.4)
IP	159.3	154.6	152.3
$10^{-5}k_7$ / $M^{-1}s^{-1}$	32	880	2800
n	2	2	2

O_2. In the event, both **12** and **13** were less reactive toward O_2 than **9**. Thus, while **9** (ca. 0.3 mM) decayed very rapidly in aerated *tert*-butyl benzene at 310 K, **12** and **13** had half-lives of 30 and 14 h, respectively, under the same conditions (while **2** and **10** showed no significant changes in their UV spectra after 24 h).[49] Because of the reactivity of **12** and **13** toward O_2, commercial interest in RTAs with these structures has focused on air-stable **11** and related dialkylamino-substituted pyrimidinols.

The pyridinol and pyrimidinol RTAs are the useful products of a happy combination of good theory, sound reasoning, and careful experimental work. Of course, even the best present-day theory is not "exact" (see, e.g., measured and calculated BDEs in Chart 6). However, it was theory and a proper understanding of desirable RTA chemistries that pointed the way to these new classes of RTAs that are structurally related to phenols but possess improved properties. In connection with this last point, it is worth noting that although the pyrimidinol, **11**, and α-tocopherol, **2**, have very similar experimental O−H BDEs, **11** is (serendipitously) twice as reactive toward peroxyl radicals. It seems unlikely that there is any change of mechanism between the phenols and the pyrimidinols. In the first place, just like the phenols, these new RTAs show substantial (primary) deuterium kinetic isotope effects when the OH group is replaced by an OD group, e.g., k_7^H/k_7^D = 10.6 for BHT[12] (**1**, providing the first mechanistic evidence for reaction 7!), 5.4 for **2**,[14] and 3.1 for **11**.[44] In the second place, just as with the phenols,[51,52] the measured rate constants for H-atom transfer from these new RTAs to attacking radicals are substantially reduced in hydrogen-bond-accepting solvents[50] (a hydroxylic H-atom involved in an intermolecular hydrogen bond is not available for transfer to an attacking peroxyl radical). Finally, phenols and pyrimidinols both have stoichiometric factors, *n* = 2.0,[48] i.e., like phenols, they trap two peroxyls per molecule (see Scheme 2). The enhanced RTA activities of pyridinols and pyrimidinols relative to phenols with similar O−H BDEs have been attributed to favorable polar effects.[44,50]

Work on these new RTAs has been extended to biomimetic systems.[53−55] As background, there was good evidence that oxidative modification of human low-density lipoprotein (LDL) could lead to an uncontrolled uptake of cholesterol by macrophages, and this, it was hypothesized, might initiate atherosclerosis. The retardation of LDL oxidation could therefore be a matter of some importance. In 1990, quantitative studies revealed that the major lipid-soluble RTA in human plasma, α-tocopherol, **2**, did not retard the (per)oxidation of the cholesteryl linoleate in the plasma's LDL particles *unless* these particles also contained ubiquinol-10 (reduced coenzyme Q_{10}, a lipid-soluble hydroquinone) or unless the surrounding medium contained ascorbate. Fortunately, a simple explanation for these unexpected results was quickly forthcoming.[56−58] The α-tocopherol within an LDL particle is insufficiently water soluble to ever leave that particle. The same is true for the α-tocopheroxyl radical formed after the tocopherol reacts with a peroxyl radical, reaction 7. If the tocopheroxyl is reduced back to α-tocopherol by ubiquinol or ascorbate, the LDL particle is protected from oxidation. However, if such reduction does not occur, the α-tocopheroxyl radical abstracts an H-atom from a cholesterol-esterified polyunsaturated lipid molecule within the LDL particle. This generates a carbon-centered radical (cf., reaction 9) which adds oxygen, and the resultant peroxyl radical will then react with an α-tocopherol molecule to form a new α-tocopheroxyl radical that continues this tocopherol-mediated peroxidation (TMP) chain reaction.[59] Quantitative work on the peroxidation of LDL supplemented with a lipid-soluble version of **12** in which the Me of the N−Me group had been replaced by a C_{16} *n*-alkyl group (**12**-*N*-$C_{16}H_{33}$) showed that endogenous α-tocopherol was "spared" until all of the (more reactive) **12**-*N*-$C_{16}H_{33}$ had been consumed.[53] Furthermore, **12**-*n*-$C_{16}H_{33}$ did not mediate LDL peroxidation. This is because the **12**-*N*-$C_{16}H_{33}$ O−H BDE is ca. 2 kcal/mol weaker than the O−H in α-tocopherol, which makes H-atom abstraction from a polyunsaturated lipid by the **12**-*N*-$C_{16}H_{33}$ aryloxyl radical extremely slow.

More significantly, an analogue of **12** has been synthesized that was designed to look more like α-tocopherol (α-T, **2**) by addition to the 2 position of both a methyl group and a phytyl group (N−TOH).[54] This compound "spares" endogenous α-tocopherol in LDL and has an improved mobility profile in model membrane systems. More importantly, N−TOH binds to recombinant human tocopherol transport protein (TTP) with a better affinity than α-tocopherol itself.[54] Since TTP mediates the movement of Vitamin E between lipid regions in vivo, e.g., between lipoproteins and cells, and between subcellular regions within cells, N−TOH and some of its derivatives, may have chemopreventive or therapeutic value.

Unfortunately, synthesis of N−TOH required 17 chemical steps, making further work with this compound all but impossible despite these exciting results.[60] For this reason, attention then turned to a less onerous synthesis of **12**, and an evaluation of the impact of the N_1 alkyl side chain length and branching on activity.[55] These compounds were then subjected to a novel experimental procedure for rapid determination of their RTA activities toward a mimic of the LDL particle and cell membrane, phosphatidylcholine liposomes.[64,65] Binding of

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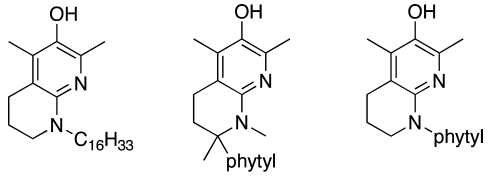
these new compounds to TTP was also measured.[55] Although side chain length and branching would have no effect on the reactivity of these **12** analogues toward ROO• (all will be ca. 30 times as reactive as **2** in homogeneous solution), the alkyl group did have a dramatic effect on stoichiometry. The more lipophilic compounds containing the larger *N*-alkyl groups trapped two ROO•, i.e., $n = 2.0$, whereas the more hydrophilic compounds with the smaller *N*-alkyl groups had $n < 1.0$, probably because they are readily autoxidized in the aqueous phase.[55] Regeneration of the lipophilic *N*-alkylated-**12** compounds within the phosphatidylcholine liposomes by ascorbate, *N*-acetylcysteine, and urate were superior to regeneration of **2** by these same sacrificial antioxidants. Even more importantly, **12** possessing *N*-alkyl groups having 8 or more carbons had affinities for TTP similar to α-tocopherol, **2**, while the *N*-phytyl derivative, **12**-*N*-phytyl, see below, had a 10-fold better binding affinity than α-tocopherol![55] Obviously, **12**-*N*-phytyl should have excellent bioavailability. In vivo work with **12**-*N*-phytyl and related compounds is clearly warranted and, in fact, currently underway.[66,74,76]

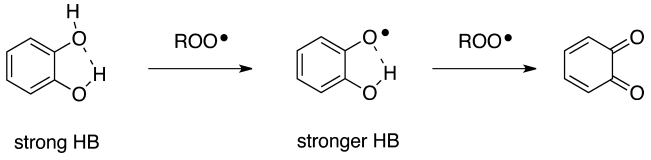


12-*N*-$C_{16}H_{33}$ N-TOH **12**-*N*-phytyl

2.4. Effects of Intramolecular Hydrogen Bonds on the RTA Activities of Phenols

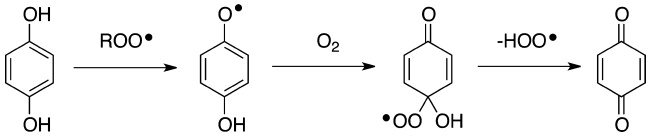
A phenol whose OH group forms an intermolecular HB to some HB acceptor (HBA) molecule is unreactive toward free radicals[51,52] but if the phenol's OH group forms an intramolecular HB, particularly a 5-center intramolecular HB (as in 2-methoxyphenol), it retains some reduced radical-trapping activity.[78] In contrast, when the aromatic system contains two OH groups connected to one another by an intramolecular HB, the O−H BDE of the "free" OH (i.e., the HBA OH group) is reduced to a greater extent than can be accounted for by the ED activity of the donor OH, that is, catechols (1,2-dihydroxybenzenes) have weaker O−H BDEs than (comparable) hydroquinones (1,4-dihydroxybenzenes), e.g., for 2,5-di-*tert*-pentylhydroquinone and 3,5-di-*tert*-butylcatechol, the O−H BDEs are 80.8 and 79.4 kcal/mol, respectively.[79] The rather low BDEs for catechols are due both to the ED character of the second (HB donor) OH group and to the increase in strength (by several kcal/mol)[79] of the intramolecular HB on going from the catechol to the *o*-semiquinone radical,[79] see Chart 7. Indeed, 3,5-di-*tert*-butylcatechol has a k_7 value about one-half that of α-tocopherol, **2**, and a "normal" stoichiometric factor of about 2.0.[80] In contrast, hydroquinones are generally relatively poor RTAs with k_7 values lower than comparable catechols and with $n < 2.0$. These low n values have been shown to be a consequence of relatively fast reactions of the 1,4-semiquinone radicals with dioxygen, reactions that appear to involve O_2 addition to the semiquinone, followed by HOO• elimination,[81] see Chart 8.

Chart 7



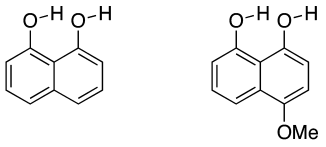
strong HB stronger HB

Chart 8



o-Semiquinone radicals actually do react with O_2 (probably in a manner similar to *p*-semiquinones, Chart 8) but somewhat more slowly. In an attempt to exploit the full beneficial effects on RTA activities of intramolecular HB formation without the deleterious effects of easy oxidation to a quinone, the RTA activities of two 1,8-naphthalenediol were explored.[82] The results, see Chart 9, showed that these two diols were more active RTAs than α-tocopherol (**2**), but probably because they were not more active than the dialkylamino-substituted pyridinols and pyrimidinols (cf. Chart 6), further work with compounds in this class appears to have been abandoned.

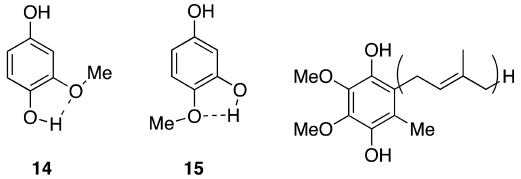
Chart 9



$10^{-5}k_7$ / $M^{-1}s^{-1}$ 43 60

"Remote" intramolecular H bonds can also influence the H-atom-donating abilities of phenols. For example, simple additivity rules would suggest that the O−H BDEs in 3-methoxy-4-hydroxyphenol, **14**, and 3-hydroxy-4-methoxyphenol, **15** (see Chart 10), would be essentially equal. However, both experiment and theory indicate that the O−H bond in **15** is ca. 2 kcal/mol stronger than in **14**, see Chart 10.[83] In agreement with this difference in BDEs, the rate constant for reaction with ROO• is three times greater for **14** than for **15**.[83] These "remote" H-bond effects are due to the strong EW properties of the aryloxyl radical's O-atom. This EW effect of O• makes the para OH group in **14** more acidic in the aryloxyl radical than in its parent phenol. This, in turn, increases the H-bond strength and hence weakens the phenolic O−H BDE in **14** and enhances k_7 relative to 3,4-dimethoxyphenol (which has $k_7 = 4.7 \times 10^5$ M^{-1} s^{-1}).[83] Conversely, the *p*-OMe group in **15** is a weaker H-bond acceptor in its aryloxyl radical, so the

Chart 10



14 **15** reduced coenzyme Q_{10}

	14	**15**
O-H BDE	80	82
$10^{-5}k_7$ / $M^{-1}s^{-1}$	7.2	2.5

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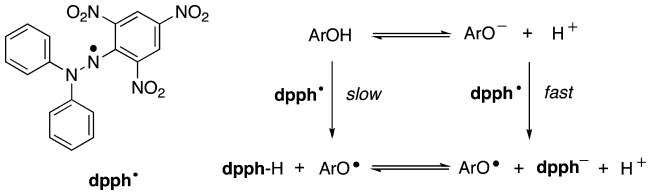
intramolecular H bond becomes weaker in the radical and k_7 is decreased. Although the remote H-bond effect does not appear to have been exploited by man, the structural similarities between **14** and reduced coenzyme Q_{10} (see Chart 10) suggest otherwise for nature!

The role of intramolecular H bonding including "remote H bonding" on the H-atom-donating abilities of phenols has been reviewed.[84]

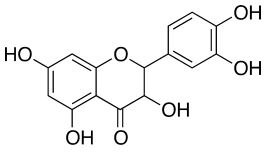
2.5. Enhancing Reactivity: Effects of Acids and Bases

Before describing this intriguing discovery it is necessary to present some background. There exists a huge (mainly academic) "industry" in which alcohol extracts from local fruits, roots, etc., are tested for "antioxidants" (on the unproven, and unlikely, grounds that all such "natural antioxidants are good for you"). The active compounds in these extracts are generally plant polyphenols, many of which are good 1-electron reducing agents, e.g., quercetin.[85] The quantities of these reducing agents in the extracts are determined by what are essentially titrations with 1-electron oxidizing agents. For experimental simplicity, these 1-e oxidizing agents are strongly colored and yield colorless products upon reduction, thus permitting simple spectrometric measurements of "antioxidants". Popular 1-e oxidants are 2,2-diphenyl-1-picrylhydrazyl, dpph$^\bullet$ (see Chart 11), and ABTS$^{\bullet+}$.[7] The simplicity of these

Chart 11. Structure of dpph• and the SPLET Mechanism



experiments disguises what is often very complex chemistry,[85−87] and the results obtained yield only the total quantities of reducing agents and have nothing to do with the relative RTA activities of the extracted compounds. Furthermore, although these experiments are frequently claimed to relate to the "H-atom donating abilities" of the extracted "antioxidants", *this is untrue*. In alcohol solvents (and, of course, water) phenols are partially ionized. Phenoxide anions, ArO^-, are oxidized very much more rapidly than the corresponding phenols, ArOH, by the electron-deficient 1-e oxidants employed in these titrations. The mechanism of these reactions has been christened sequential proton-loss electron transfer, SPLET (Chart 11).[52] This mechanism can occur only in solvents that support at least a partial deprotonation of the phenol. SPLET is not the direct H-atom transfer from the RTA to ROO$^\bullet$ as discussed earlier in this review, and therefore, experiments carried out under conditions that permit the SPLET mechanism to occur have little or nothing to do with antioxidants. The fast SPLET process can be suppressed by limiting deprotonation of the phenol. Complete suppression of SPLET permits the very much slower H-atom transfer to be observed. Experimentally,



quercetin

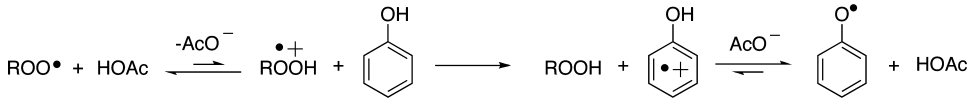
SPLET suppression is most readily achieved by addition of acetic acid to the alcohol solvent.[52,86,87]

In 2009, in a collaboration between one of us and Valgimigli,[36] an attempt was made to minimize any contribution from the SPLET mechanism to the ROO$^\bullet$ + ArOH reaction during the azo-initiated autoxidation of styrene at 30 °C in acetonitrile containing 1% water by addition of acetic acid,[52] AcOH. Unexpectedly, addition of this acid produced a dramatic decrease in the rates of oxygen uptake in these already inhibited autoxidations, although AcOH had no effect on phenol RTA activities in the nonpolar solvent, chlorobenzene. Acetic acid was more effective than stronger acids, as had been found in earlier studies of SPLET suppression.[52] The AcOH-induced enhancement of inhibition increased as [AcOH] increased and was very large (factors of 100−1000 for the ratios of the inhibition rate constants with/without AcOH versus AcOH concentration) for several phenols and a pyrimidinol. These RTA improvements became greater as the temperature was lowered, suggesting that acid catalysis of reaction 7 involved an endothermic pre-equilibrium. The mechanism advanced to explain these results[36] is shown in Scheme 3. It involves protonation of the peroxyl radical (explaining the need for a polar solvent and the existence of an endothermic pre-equilibrium), followed by a rate-determining electron transfer from the phenol to the hydroperoxide radical cation. Such a mechanism should operate best with weak organic acids that are not strong enough to protonate the phenol and impair electron transfer. Consistent with this mechanism is an *inverse* deuterium kinetic isotope effect. Thus, for **3** and 3,5-di-*tert*-butyl catechol in the absence of AcOH, k_7^H/k_7^D = 6.4 and 4.6, respectively, but in the presence of this acid these ratios fall to 0.9 and 0.6, respectively.[36] The potential significance of these results for RTAs used industrially and by Nature was considered briefly.[36] The solvent that would appear to be required for this acceleration of ArOH + ROO$^\bullet$ reactions, acetonitrile, means that this procedure remains no more than an idle RTA "curiosity"—to date!

2.6. Synergy and Regeneration of Phenolic RTAs

Before leaving phenol RTAs, it should be recalled that Nature discovered two chemistries that "extend" the utility of its major lipid soluble RTA, **2**, by reducing the α-tocopheroxyl radical back to α-tocopherol. This can occur by means of either a lipid-soluble reducing agent (e.g., reduced coenzyme Q_{10}) or a water-soluble reducing agent (e.g., ascorbate, vitamin C).[59] These in vivo methods for "regeneration" of vitamin E involve "sacrificial" reducing agents. Similar methods involving "sacrificial" *and cheap* BHT (**1**, Chart1) have long been used to regenerate the much more effective, but also much more

Scheme 3. Proposed Mechanism for the Acid-Catalyzed Reaction of Phenols with Peroxyl Radicals



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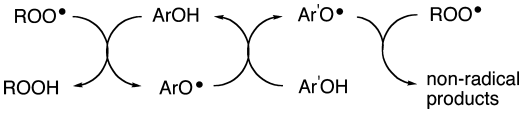
expensive, diarylamine RTAs in the lubricating oils of combustion engines.

2.6.1. Synergy in Phenolic RTAs. While the observation was made long ago that certain mixtures of RTAs are much more effective than the additive contributions of the individual components,[7] the relevant kinetic and thermodynamic parameters that were expected to underpin the synergism[15] were sparse until much later—the kinetic data coming on the scene in the 1980s[13,14] and the thermodynamic data in the 1990s.[79,88,89] With these parameters in hand, Valgimigli and co-workers were able to clarify the framework for synergism in homogeneous solutions; this is illustrated for two phenolic RTAs in Scheme 4.[90,91]

Scheme 4. Synergistic Behavior in a Binary RTA Mixture

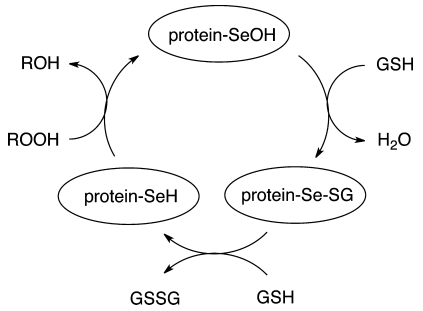


In this scheme, the most reactive phenol (ArOH) undergoes H-atom transfer to peroxyl radicals and the less reactive phenol (Ar′OH) is used to regenerate ArOH. As such, regeneration requires a favorable equilibrium for the ArO•/Ar′OH reaction couple and fast H-atom exchange between phenols and phenoxyl radicals; otherwise, ArO• will react with peroxyl radicals. An example of a very efficient coantioxidant system comprising of conventional phenols makes use of the highly reactive α-T, **2** ($k_7 = 32 \times 10^5$ M^{-1} s^{-1}, O−H BDE = 77.2 kcal/mol), and the much less reactive 2,6-di-*tert*-butylated hydroxyanisole, dBHA ($k_7 = 1.1 \times 10^5$ M^{-1} s^{-1}, 77.0 kcal/mol). When used in combination, the autoxidation kinetics are indistinguishable from those of an autoxidation inhibited by α-T alone but with stoichiometries reflected by the total amount of RTA (i.e., [α-T] + [dBHA]).

In more recent work, this concept was exploited to design coantioxidant systems employing highly reactive pyridinol or pyrimidinol RTAs in combination with less reactive, but much less expensive, phenolic antioxidants. As expected, provided that pyridinols/pyrimidinols were partnered with phenols possessing lower O−H BDEs, antioxidant mixtures were characterized by kinetics that were indistinguishable from those of the pyridinols/pyrimidinols alone but with stoichiometries reflected by the total amount of RTA, not just of the more reactive one.[92] Particularly useful combinations included those of simple (monosubstituted) pyridinols or pyrimidinols, which possess relatively strong O−H bonds, but very high reactivities, with dBHA or BHT.

2.6.2. Regeneration of Alkyl-Chalcogen-Substituted Phenols by Sacrificial Reductants. Engman and co-workers published a fascinating series of papers on the syntheses and antioxidant "profiles" of alkyl chalcogen-substituted phenols.[93−101] The intention was to build on, and hopefully improve on, some of Nature's most effective RTA/hydroperoxide-decomposing preventive antioxidant "couples", e.g., α-tocopherol (**2**)/glutathione peroxidase, GPx and/or superoxide dismutase/catalase. The GPx's are a small family of selenocysteine-containing enzymes that catalyze decomposition of hydrogen peroxide and organic hydroperoxides to water and alcohols, respectively.[8] These enzymes employ the water-soluble tripeptide (γ-GluCysGly) known as reduced glutathione (GSH) as a stoichiometric reducing agent. The GSH is oxidized to the glutathione disulfide GSSG by the mechanism shown in Scheme 5.

Scheme 5. Catalytic Cycle of Glutathione Peroxidase



Engman and co-workers were attempting to combine a phenol RTA and a substituent that exhibited GPx-like hydroperoxide-decomposing activity into a single molecule. The authors of this review admit that they are not fans of "dual" antioxidants that combine two types of antioxidant activity into a single molecule. A large synthetic effort results in a molecule containing the two antioxidant active groups in a 1:1 molar ratio. Unless there is some serendipitous intramolecular interaction between the two antioxidant functional groups, the same antioxidant activities could be achieved much more cheaply and readily using the two antioxidant groups in a 1:1 molar ratio in two separate compounds. Moreover, it seems improbable that a 1:1 molar ratio of the two classes of antioxidants will be the optimum molar ratio for most systems subjected to oxidative stress. However, in the present case, Engman's hard work and persistence were rewarded by his discovery of an unprecedented, and still not completely understood, intramolecular synergistic antioxidant effect: *o*-alkyl-tellurium-substituted phenols, but *not* their para-substituted isomers, have exceptional antioxidant properties, see below.

Before launching into an account of Engman's organotellurium antioxidant work, it seems appropriate to tell an old, but previously untold, cautionary tale about organoselenium antioxidants. In the 1930s, oxidative degradation of automobile engine oils was retarded by organosulfur compounds, both those naturally present in the oil and compounds that were added and had been chosen on the basis of oil solubility and price, only. A chemist, George Denison, at Chevron Oil Co. (California) discovered that although dialkyl selenides were more expensive than the dialkyl sulfides then in use, they provided huge improvements in the distances that could be driven between oil changes, changes required because of viscosity increases that eventually interfered with engine lubrication. The toxicity of selenium was known[102] but was no deterrent[103] to its use in engine oils. Great plans to shift lube oil formulation from organosulfur to organoselenium additives were only abandoned when it was realized that the world's entire production of selenium would be insufficient for California's cars alone![104]

There are no known tellurium-containing enzymes,[105] and tellurium does not appear to be an essential element. Tellurium has a reputation for being toxic to humans,[106] and whether justified or not,[100] such a reputation should serve as a warning to be extremely careful when handling (let alone ingesting) any organotellurium antioxidant, whatever its claimed potency. Moreover, industrial exploitation of tellurium-based antiox-

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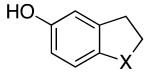
idants appears to face one of the same problems as were faced by selenium-containing antioxidants as automobile lube oil additives: its supply. Tellurium is as rare in the earth's crust (27 ppb) as silver or gold, but it is cheap and readily available because it is a byproduct of copper refining (ca. 1 lb. per ton of ore) and has few uses. However, if a major use for tellurium were to be discovered this availability would vanish overnight.

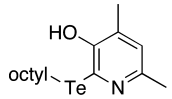
Engman's initial results[93] must have been disappointing. The antioxidant properties toward 36 mM linoleic acid of 40 μM of the alkyl-chalcogen-substituted phenols, **16**–**19**, were compared with those of 40 μM α-tocopherol, α-T (**2**), in water/chlorobenzene (1:1 v/v) containing a PhCl-soluble azo initiator at 42 °C. To this system could also be added 1 mM (which is 25 times the amount of the phenol) of a water-soluble, simplified analogue of GSH, *N*-acetylcysteine, NAC, to serve as a "sacrificial" reducing agent which might enhance the RTA and/or the GPx-like activities of these compounds. (Using a different two-phase system, Barclay[107] had shown previously that GSH does not inhibit lipid autoxidation and does not extend the α-T-induced induction period.) None of the synthesized antioxidants were as effective RTAs as α-T, and the tellurium compound, **19**, showed no antioxidant activity at all in the absence of NAC. On the other hand, only **19** showed peroxidase activity, accelerating the rates of decomposition of H_2O_2, Me_3COOH, and $PhCMe_2OOH$ in the presence of NAC by factors of 100–300 over the rates of their spontaneous decomposition.[93]



X = O (**16**)
S (**17**)
Se (**18**)
Te (**19**)

The next Engman paper[94] marks the start of another fruitful collaboration involving the antioxidant chemists from Bologna. For 1-seleno-α-T the O–H BDE was determined by the radical equilibrium EPR technique[88,89] and the rate constant for ROO$^\bullet$ radical trapping, k_7, was determined by the classical inhibited oxidation of styrene method.[12] Earlier work by others[108] had shown that 1-thio-α-T was less reactive than α-T, and the same proved to be true for 1-seleno-α-T.[94] Moreover, the 1-seleno-α-T was, like α-T, not regenerable by NAC.

The work on "multifunctional catalytic" antioxidants continued in the same vein in 2007 with some more chalcogen-substituted phenols[95,96] and an arylamine[96] but without any major breakthroughs. However, in 2008 perseverance paid off during a preliminary study of a large family of chalcogen-substituted pyridinols.[97] In the two-phase system, not one of the eight alkyl-tellurium-substituted pyridinols tested showed any antioxidant activity in the absence of NAC, i.e., these compounds did not produce an induction period nor was there any significant reduction in the initial rate of linoleic acid oxidation.[97] However, in the presence of the usual 1 mM NAC, some of these compounds became better RTAs than α-T, most notably **20** for which the duration of the induction period in the two-phase system could be increased by increasing [NAC], ending only when the NAC had been consumed, i.e., the duration of the induction period with **20** was limited only by the availability of the thiol reducing agent (NAC)! In addition, the duration of the induction period with 1 mM NAC was the same at 20 μM **20** as at the standard 40 μM (>400 min), decreasing to 310 min at 10 μM, and becoming unobservable at 5 μM **20**. Clearly, *oxidized* **20** in the lipid phase can be reduced back to **20** by NAC in the aqueous phase. However, in contrast to the α-T and ascorbate couple in other two-phase systems,[109] the oxidized form of **20** that is reduced *is not its pyridinoxyl radical*, see below. The isomeric pyridinol, **21**, was a much poorer RTA than **20**.



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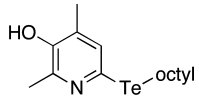
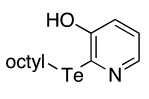


21

More detailed studies of **20**, **21**, and related compounds followed.[98−101] In a homogeneous chlorobenzene/styrene (1:1, v/v) solution, the rate constant for ROO$^\bullet$ trapping by **20** k_{inh} was 92×10^5 M^{-1} s^{-1}; note this is not reaction 7, and *hence, it is not* k_7, see below. This rate constant is three times greater than k_7 for ROO$^\bullet$ trapping by α-T. However, the stoichiometric factor, *n*, for ROO$^\bullet$ trapping by **20** was only 0.4 (vs 2.0 for α-T).[13,14,99] Another pyridinol with an alkyltellurium substituent ortho to the OH group, **22**, also had a very high k_{inh} (100×10^5 M^{-1} s^{-1}) and low *n* value (0.5), whereas k_{inh} was only 8×10^5 M^{-1} s^{-1} for the para isomer, **23**, and the *n* value was only 0.3.[99] More importantly, addition of *N*-*tert*-butoxycarbonyl cysteine methyl ester, LipCys (a lipid-soluble analogue of NAC), to the homogeneous solution containing **20** extended the induction period in direct proportion to the added [LipCys] but more or less independent of [**20**].[99] LipCys did not change the induction period produced by α-T. Interestingly, although the telluroxide derivative of **22**, i.e., **24**, did not, by itself, inhibit styrene autoxidation, upon addition of LipCys **24** became just as good an antioxidant as **22**. Moreover, once **22** had been consumed and inhibition had ended, inhibition could again be induced by addition of an aliquot of LipCys, and this "regeneration" of the RTA **22** could be repeated many times.[99] The stoichiometric factor for LipCys was ~0.26 when used with **22**, **20**, and **24**. Clearly, a large fraction of the thiol is consumed in reactions not leading to chain termination. This is hardly surprising in view of the well-known ability of thiyl radicals, RS$^\bullet$, to add to styrene, a reaction that gives a carbon-centered radical which will add O_2 and continue the oxidation chain. (This is one step in the thiol–olefin co-oxidation (TOCO) reaction.)[110]



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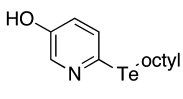

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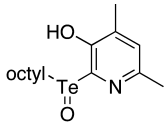

24

Pyridinols with an alkyltellurium substituent ortho to the OH group are much better RTAs than their para isomers. Additional experiments showed that this ortho effect is also present in phenols.[100] For example, in the homogeneous styrene/chlorobenzene system, 2-octyltellurium-4-methoxy-6-*tert*-butylphenol, **27**, is an outstanding RTA with a k_{inh} value three times greater than the k_7 for α-T but 2,6-di-*tert*-butyl-4-phenoxypropyltelluriumphenol, **29**, is a very poor RTA, see Table 1. The other two *o*-alkylchalcogen phenols, i.e., the 2-octylthio, **25**, and 2-octylselenium-4-methoxy-6-*tert*-butylphenol, **26** are also very poor ROO$^\bullet$ traps (see Table 1). These compounds had been synthesized earlier in order to study the *o*-alkyltelluride effect on O–H BDEs[98] by the EPR equilibrium method because this technique has requirements that were not

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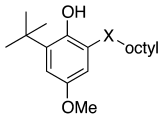
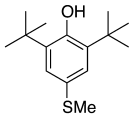
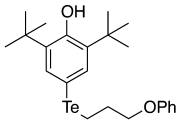
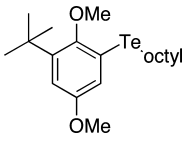
Table 1. Experimental O−H BDEs (in kcal/mol), Inhibition Rate Constants (in M^{-1} s^{-1}), and Stoichiometric Factors Determined in PhCl/styrene for Some Alkylchalcogen-Substituted Phenols

					
	X=S	X=Se	X=Te		
	25	**26**	**27**	**28**	**29**
BDE (kcal/mol)[a,b]	80.6	79.8	78.9	78.0	78.6
$10^{-5}k_{inh}(k_7)$ /$M^{-1}s^{-1}$ [c]	0.08	0.2	100	0.3	0.09
n	1.9	2.1	0.4	2.0	0.7

[a]From ref 98. [b]For comparison, the O−H BDE and $10^{-5} \times k_7$ (M^{-1} s^{-1}) values are 80.3 and 6.4 (n = 1.8), respectively, for 2-*tert*-butyl-4-methoxyphenol.[98] [c]From ref 100.

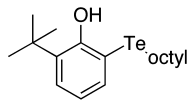
met by the simpler pyri(mi)dinols (e.g., **10**−**13**).[98] Their O−H BDEs are given in Table 1, together with their inhibition rate constants, k_{inh} (k_7), and stoichiometric factors, n.[100] Since an *o*-alkyltellurium group does not produce a dramatic reduction in a phenol's O−H BDE, the reason for the outstanding ROO• trapping properties of the *o*-alkyltellurium-phenols and -pyridinols must be sought elsewhere.

The behavior of the alkylchalcogen-substituted phenols in Engman's two-phase system mirrored that of their pyridinol counterparts.[100] This ground-breaking work eliminated the classic (witness the α-T/ascorbate couple)[111] interpretation of the NAC-induced increase (or occurrence) of an inhibition period by alkyltellurium-substituted phenols (or pyridinols) as being due to "regeneration" of the RTA by reduction of the phenoxyl (pyridinyloxyl) radical's O• to an OH group. The presence or absence of NAC had no effect on the initial rate and induction period with the ortho-substituted sulfur, **25**, and selenium, **26**, compounds. However, addition of NAC to the system containing the ortho-tellurium compound, **27**, gave an even lower initial rate and longer induction period than those obtained with α-**T**, while the antioxidant performance of the para-tellurium compound, **29**, now became comparable to that of α-**T**.[100] The NAC-enhanced RTA activities of the two alkyltellurium compounds, **27** and **29**, were quite reasonably assigned to the presence of traces of hydroperoxides in the linoleic acid substrate. These hydroperoxides "instantaneously" converted the RTA-active alkyltellurium phenols to the RTA-inactive alkyltelluroxide-substituted phenols. What is even more remarkable was that all the signs of a NAC-induced "regeneration" also occurred with a compound that contained no *aromatic OH group*, the methyl ether of **27**, i.e., **30**![100]

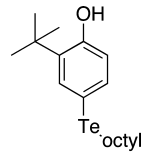


30

In the homogeneous styrene autoxidation, **30** exhibited *no RTA activity*, as expected, and the same was true in the two-phase system in the absence of NAC. However, in the presence of the usual 1 mM NAC, **30** (40 μM) gave an initial rate and induction period that were almost indistinguishable from those obtained with the same concentration of α-T. Clearly, this alkyltellurium-substituted aromatic has an RTA activity that does not arise from an OH group. Whatever this new RTA process for **30** may be, it seems likely also to occur with the tellurium-substituted phenols and pyridinols and to account for their extraordinarily high RTA activities. In this connection, RTA activity by H-atom transfer in the 2-*tert*-butyl-6-(octyltelluro)phenol, **31**, and 2-*tert*-butyl-4-octyltellurophenol, **32**, inhibited autoxidation of styrene can be ruled out by insignificant OH/OD deuterium kinetic isotope effects, k_{inh}^{H}/k_{inh}^{D} = 1.2 ± 0.4.[101] It can also be ruled out by the PhCl/MeCN kinetic solvent effect (KSE) for inhibition of styrene autoxidation by these two phenols.[101] If inhibition was due to H-atom transfer, as is the case for α-T, k_{inh} would be smaller in MeCN than in PhCl.[52] However, **32** showed no KSE (k_{inh} = 16 × 10^5 M^{-1} s^{-1}), and **31** had an "inverted" KSE with a larger k_{inh} in MeCN than in PhCl (350 × 10^5 vs 100 × 10^5 M^{-1} s^{-1}).



31



32

In contrast to all other phenols, the rate-determining step in the reactions of ROO• with **31** and **32** (not to mention **27** and **30** in the two-phase system) do not involve abstraction of a phenolic H-atom. By default, they must instead involve attack of the ROO• on the tellurium atom with (eventual) formation of a telluroxide. Such a reaction has been shown to proceed at rates close to diffusion controlled (k = 10^8 M^{-1} s^{-1}) for diaryl tellurides.[112]

Reactions of MeOO• with 2- and 4-methyltellurophenols (simpler analogues of **31** and **32**) were explored by DFT.[101] For both compounds, the rate-determining step involved a low-energy oxygen-atom transfer to give the telluroxide-phenols and the MeO• radical, with the latter then abstracting the phenolic H-atom to form methanol and the phenoxyl radicals. The much faster reaction of *o*-alkyltellurophenols compared with their para isomers was dismissed with these words: "Although the overall energetic of the reactions of the ortho- and para-substituted phenols are similar, the ortho compound has a definite advantage in that HAT can occur intramolecularly between the methoxyl radical and the phenolic hydroxyl group without dissociation", that is, H-atom abstraction in the ortho case "relies on the in-cage reaction of the alkoxyl radical with the phenolic OH".[101] We are not convinced of the validity of such arguments.

These reactions clearly deserve more detailed theoretical study. In the meantime, we note that *o*-alkyltelluro-phenols

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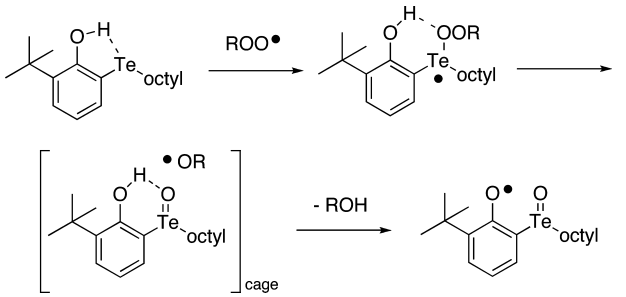
(and pyridinols) are expected to possess an intramolecular H bond, Scheme 6. Attack of ROO• on the divalent Te will

Scheme 6. Proposed Mechanism of RTA Activity of *o*-Alkyltelluro Phenols



probably produce Te−O bonding via a lone pair on the O• and simultaneous transfer of an electron from the Te valence shell to the O• SOMO (to prevent significant charge separation). A trivalent tellurium-centered radical with an expanded valence shell of nine electrons will be produced. It seems reasonable to expect that such a valence shell expansion would be facilitated by the presence of an OH---Te hydrogen bond, thus accounting for the higher reactivities of the ortho over the para alkyltellurophenols (and pyridinols). As already proposed,[101] the Te•O−OR bond subsequently cleaves to yield the telluroxide and an alkoxyl radical. The latter may either diffuse into the bulk solution to continue the oxidation chain or abstract the H-atom, in cage, from the OH group to terminate a chain. Propinquity ensures that, for this highly exothermic reaction, the H-atom abstraction will be more probable for the ortho than for the para alkyltelluro compounds, thus accounting for the higher *n* values found for the ortho isomer. Further experimental and theoretical work on tellurium-containing antioxidants promises to be very interesting.

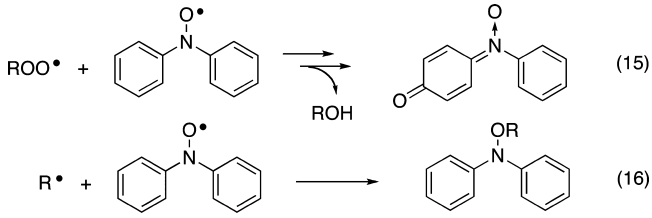
3. PEROXYL RADICAL TRAPPING BY DIARYLAMINES AND CLOSELY RELATED COMPOUNDS

At first sight, the RTA behavior of diarylamines, Ar_2NH, might appear similar to that of phenols. At 65 °C, they trap two peroxyl radicals[27] and donate a hydrogen atom from their NH group to a peroxyl radical in the rate-determining step of inhibition, e.g., for diphenylamine, Ph_2NH, $k_{13}^{H}/k_{13}^{D} = 3.0$.[27] However, while the resultant diphenylaminyl radical, like a phenoxyl radical, does "capture" a second ROO•, it can use its N• atom to do this. The resultant $ROONAr_2$ adduct immediately decomposes to yield a nitroxide, $Ar_2NO^{\bullet}$, that can be readily observed by EPR spectroscopy[113,114] and a highly reactive alkoxyl radical, RO•, reaction 14.[115] This radical will abstract H from RH and initiate a new chain, so reaction 14 is not chain ending.

$$ROO^{\bullet} + Ar_2NH \rightarrow ROOH + Ar_2N^{\bullet} \quad (13)$$

$$ROO^{\bullet} + Ar_2N^{\bullet} \rightarrow RO^{\bullet} + Ar_2NO^{\bullet} \quad (14)$$

With Ph_2NH as the RTA under typical experimental conditions at temperatures of 65−69 °C, the efficiency of conversion of Ph_2NH to $Ph_2NO^{\bullet}$ is 30−33% for the autoxidation of cumene.[113,114] Since $n = 2.0$ at the temperatures under consideration,[27] a second radical must be trapped. This is probably due to ROO• capture by the aromatic ring, with formation of a quinone nitrone, reaction 15. There may also be some trapping of the carbon-centered radical R• derived from the substrate, RH, eq 16. This "cross" radical/radical combination occurs at rates close to diffusion control.[117]



The most intriguing thing about diarylamine RTAs is that at temperatures >100 °C their stoichiometric factors (*n* values) increase (rather than decrease, as is the case for phenol RTAs). For example, as early as 1978 an *n* value of 40 (!) was reported for the Ph_2NH-inhibited autoxidation of a paraffin oil at 130 °C.[118] Several difficult to believe "explanations" (involving what might be most politely described as "unprecedented" chemical reactions that are of only historical interest today) have been proposed for these huge *n* values. What is almost certainly the correct explanation for these large *n* values was forthcoming only in 1995. In that year, Korcek and co-workers[119] reported, as expected,[113,114] that when 0.38 mM of an oil-soluble diphenylamine (4,4′-dioctyldiphenylamine, the major diarylamine used commercially as an RTA) was added to autoxidizing hexadecane at 160 °C, the corresponding nitroxide was formed. The nitroxide concentration passed through a maximum (0.03 mM, i.e., ca. 9% of the initial amine concentration) as the reaction proceeded. These workers reports were *totally unexpected*. When virtually the same concentration of the nitroxide was added in place of the amine, *not only was the oxidation suppressed to approximately the same extent as by the amine but also the parent amine, 4,4′-dioctyldiphenylamine, was formed in >54% yields*![119] The concentration of the amine also, of course, passed through a maximum as the reaction progressed. It was demonstrated that at temperatures above 120 °C *N*-(*sec*-hexadecyloxy)-4,4′ dioctyldiphenylamines decomposed to yield the amine and hexadecanones, eq 17. This proof of the reduction of diarylnitroxides to the corresponding diarylamines via decomposition of the nitroxide + *sec*-alkyl radical coupling product, reaction 16, provided a sound explanation for the high *n* values of these diarylamine/diarylnitroxide RTAs at temperatures > 120 °C.

$$Ar_2NOCH(R)(R') \rightarrow \{Ar_2N^{\bullet} + {}^{\bullet}OCH(R)(R')\}_{cage}$$
$$\rightarrow Ar_2NH + O{=}C(R)(R') \quad (17)$$

The catalytic RTA cycle involves reactions 13, 14, 16, and 17. It leads to large but not infinite *n* values, not infinite because of side reactions. The main side reactions appear to involve oxidation of the aromatic rings, the aminyl radical being oxidized to a quinone−imine, and the nitroxide being oxidized to a quinone−nitrone, reactions 18 and 19, respectively. Indeed, although peroxyl radicals do not react with di-*tert*-alkyl nitroxides[120] (at least in the absence of acid,[36] see later), they do react with diarylnitroxides, the rate constant for ROO• trapping by bis(4-methoxyphenyl) nitroxide at 65 °C having been estimated to be 5×10^4 M^{-1} s^{-1}.[120]

"Side" reactions 18 and 19 are going to be a "fact of life" for diarylamine RTAs simply because both the aminyl radical and

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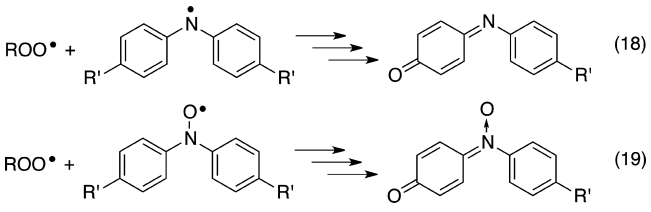


its nitroxide have significant spin density at the ortho and para positions of their aromatic rings.

Two improvements to the standard diarylamine RTAs of commerce would result from a greater stabilization of the diarylaminyl radical, $Ar_2N^•$. First, the rate constant for ROO• trapping would be increased (i.e., a faster k_{13}). Second, the intermediate alkoxyamine would undergo a more facile N−O bond homolysis (i.e., a faster k_{17}, note that the alkoxyl part of the alkoxyamine comes from the substrate and cannot be changed). Stabilization of the $Ar_2N^•$ radicals must, of course, be achieved without lowering the oxidation potentials of their Ar_2NH parents to the point where the Ar_2NH reacts directly with dioxygen and hydroperoxides. Thus, the obvious question becomes can diarylamine RTAs be improved by following the approach that so successfully weakened phenol O−H bonds, raised phenol IPs, and made much better phenolic RTAs, that is, will changing from diphenylamines to dipyridylamines or dipyrimidinylamines and placing a dialkylamino substituent para to the NH group improve RTA performance?

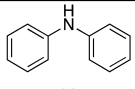
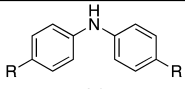
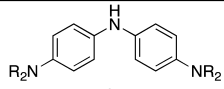
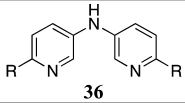
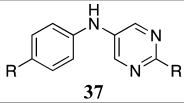
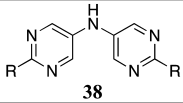
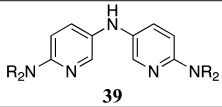
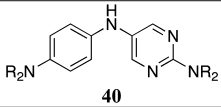
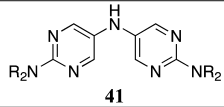
In the event,[39,121,122] the dialkylamino-substituent effects on N−H BDEs and inhibition rate constants, k_{13}, were substantial, although not as great as for phenols, pyridinols, etc. This is because PhN• is not as strongly electron-withdrawing as O•,[18,19] so that increasing the electron density in the aromatic ring has a smaller effect on N−H BDEs than on the O−H BDEs in phenols. However, two rings are available for modification. Extensive CBS-QB3 calculations of N−H BDEs and IPs pointed the way[121] and were followed by the syntheses of libraries of air-stable, heteroring-substituted, Ar_2NH compounds.[122] The RTA activities (k_{13} at 37 °C), N−H BDEs, and oxidation potentials of these compounds were then experimentally investigated;[39,121] see Table 2 for a sample set of the derivatives examined. Note that the experimental N−H BDEs of **35**, **39**, and **41** (all fairly easily determined by the ESR equilibrium technique because of their molecular symmetry) increase along this series (as expected) but only by 0.8 kcal/mol, which is within the experimental errors.[39,121] Differences in N−H BDEs are much smaller than differences in E^o values. This is consistent with the expectation that N-atom incorporation into an aryl ring will destabilize a diarylamine radical cation, $(Ar_2NH)^{•+}$, more than the corresponding diarylaminyl radical, $Ar_2N^•$.[39]

Rate constants (k_{13}) for the reaction with ROO• of the most electron-rich diphenylamine (**35**) could not be determined because this amine reacted immediately upon exposure to air or a hydroperoxide to give intensely colored products,[39] behavior that is reminiscent of the behavior of dialkylaminophenols, see reaction 12. Much more importantly, reactions **39**, **40**, and **41** with ROO• lived up to expectations by proceeding at rates that approach the diffusion-controlled limit.

Measurements of k_{13} by peroxyl radical clock methodology[123−125] over the temperature range 37−95 °C yielded E_a = 2.5 kcal/mol and $\log(A_{13}/M^{-1}\ s^{-1})$ = 6.9 for **33**, while the unsymmetrical pyrimidinyl dialkylaminophenyl amine $C_4N_2H_3NHC_6H_4NR_2$ (not shown in Table 2) had $k_{13} \approx 100 \times 10^5\ M^{-1}\ s^{-1}$ essentially independent of temperature.[39,121] Thus, $\log(A_{13}/M^{-1}\ s^{-1})$ must be ∼7 for these reactions, which further confirms that compounds **39**, **40**, and even **41**, react with ROO• at close to the diffusion-controlled limit.[39,121]

Although the N−H BDEs of the last three compounds are 1.3−1.9 kcal/mol *stronger* than the O−H BDE in α-T (77.3 kcal/mol measured under the same conditions), the amines all react with ROO• more rapidly than the α-T (for which k_7 was found to be $71 \times 10^5\ M^{-1}\ s^{-1}$ under the same conditions). Theory indicated that the reactants adopt a roughly "eclipsed" syn arrangement in the transition state for reaction 13,[39,121] similar to the reagents in reaction 7. The reason(s) for reaction 13 being faster than a thermodynamically equivalent reaction 7 remain to be firmly established. However, it seems probable that polar effects cause the barrier to be lower when H-atom

Table 2. Experimental N−H BDEs (in kcal/mol), Standard Reduction Potentials (in V vs NHE in MeCN), and Values of k_{13} Determined Using the Peroxyl Radical Clock Method (in $M^{-1}\ s^{-1}$ in PhCl)[a]

			
	33	**34**	**35**
N-H BDE	84.7	82.2	78.4
E^o	1.1[a]	1.02[a]	0.34
$10^{-5}k_{13}$	0.2	1.8	unstable
			
	36	**37**	**38**
N-H BDE	83.1	n/a	84.1
E^o	1.12[a]	1.13[a]	1.55[a]
$10^{-5}k_{13}$	0.9	1.3	0.3
			
	39	**40**	**41**
N-H BDE	78.8	79.0	79.2
E^o	0.44	0.44	0.65
$10^{-5}k_{13}$	340	370	180

[a]Data selected from refs 39 and 121. [b]Anodic peak potentials, E_{pa}.

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transfer occurs between two different heteroatoms, e.g., [N---H•---O ↔ $N^{\delta+}$---H•---$O^{\delta-}$]‡ than when it occurs between identical atoms, e.g., [O---H•---O]‡. Or, in MO speak, the π-MOs of diarylamines are higher in energy than those of phenols, which provides better orbital overlap for the amines with the peroxyl's π-SOMO.[39,121] Whether these heterocyclic diarylamines are reactive at the elevated temperatures where their predecessors are most useful remains to be seen.

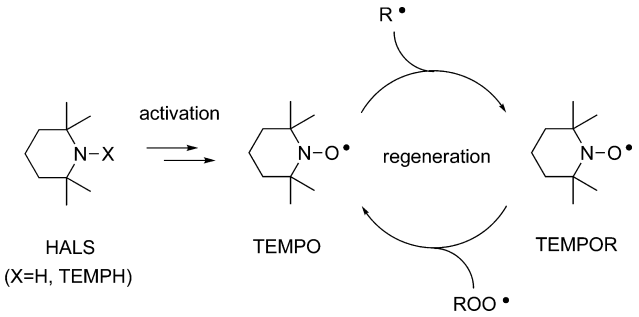
4. DI-*TERT*-ALKYL AMINE, NITROXIDE, AND ALKOXYAMINE RTAs

4.1. Hindered Amine Light Stabilizers, HALS

The oxidation products of many phenolic RTAs and all diarylamine RTAs are very intensely colored. This attribute precludes their use as stabilizers of numerous polymers that will be subjected to (photo)oxidative stress. Fortunately, traditional RTAs can be replaced in polymers by (essentially noncolor-forming) di-*tert*-alkylamines[126] and various derivatives thereof. These are generally based on 2,2,6,6-tetramethylpiperidine (TEMPH) and are referred to as hindered amine light stabilizers (HALS). For many polymeric materials HALS provide remarkable protection against oxidation both at the high temperatures of processing[127] and at the much lower temperatures of use.

HALS have long been known to owe their effectiveness as RTAs to their high stoichiometric factors[127] which demand recycling of the HALS-derived, ring-substituted nitroxides since these are the active antioxidants. The Denisov cycle[128] (see Scheme 7) has long been accepted for this recycling, but its detailed mechanism remained obscure on two important points until recently.[129]

Scheme 7. The Denisov Cycle



First, what is the mechanism of *activation* of the HALS, i.e., their conversion to the nitroxide, see Scheme 7. This obviously will depend on the chemical structure of the X group. However, this step has usually been described in general terms rather than by chemically plausible mechanisms.[128,130,131] Second, what is the mechanism of "regeneration" of the nitroxide from the alkoxyamine, TEMPOR? This question has produced more than a dozen different "answers", containing over 30 individual reactions.[129] These many proposed mechanisms had only one thing in common: *implausibility*. Not only were most of these proposals unacceptable to mechanistic chemists but also recent ab initio molecular orbital theory and density functional theory calculations showed impossibly high kinetic and thermodynamic barriers.[129,132] Even the thermochemically "easiest" of these proposals[133] (discovered in the first of these two computational studies[132]) had an essentially insurmountable activation barrier (~35 kcal/mol) for one of its steps. More importantly, this "least bad" pathway[133] does not explain the experimentally observed formation of secondary piperidines, e.g., TEMPH, during thermo- and photo-oxidation of organic materials containing TEMPO-based HALS.[134−136]

4.1.1. HALS Activation. The first commercial HALS were either piperidine-ring-substituted secondary amines or their *N*-methyl derivatives (represented hereafter only by their active head groups, TEMPH and $TEMPCH_3$, respectively.) The first step in their conversion to the TEMPO involves an H-atom abstraction by an oxidizing radical derived from the polymer, i.e., ROO• or RO•. Of these two, the more plentiful are the less reactive peroxyl radicals for which the calculated Gibbs free energies of activation, $\Delta G^{\ddagger}$, are fairly large but definitely not insurmountable, e.g., 14 and 13 kcal/mol for the ROO• reactions 20 and 21, respectively.[129]

$$ROO^{\bullet}/RO^{\bullet} + TEMPH \rightarrow ROOH/ROH + TEMP^{\bullet} \quad (20)$$

$$ROO^{\bullet}/RO^{\bullet} + TEMPCH_3 \rightarrow ROOH/ROH + TEMPCH_2^{\bullet} \quad (21)$$

However, an interesting property of polymers (often ignored) is that they tend to concentrate "impurities" (such as HALS, the ROOH oxidation products, and photolabile ketones formed during processing), "squeezing" them into microdomains and out of the bulk polymer. Alkoxyl radicals will be formed in these domains by photo- and, Fe^{II}-catalyzed decomposition of ROOH. These highly reactive alkoxyl radicals (e.g., $\Delta G^{\ddagger}$ was calculated[129] to be 5.3 kcal/mol for the RO• reaction 20) will therefore tend to be formed in these microdomains and therefore in the immediate neighborhood of the HALS. It seems likely that *N*-methyl-HALS activation will involve both RO• and ROO•.

Activation of *N*-(*n*-alkyl)-HALS has not, apparently, been discussed, but a simple mechanism would involve reaction with a hydroperoxide to form an amine *N*-oxide followed by Cope elimination.

$$TEMPCH_2CH_2R' + ROOH \rightarrow TEMP(\rightarrow O)CH_2CH_2R' + ROH \quad (21a)$$

$$TEMP(\rightarrow O)CH_2CH_2R' \rightarrow TEMPOH + CH_2{=}CHR' \quad (21b)$$

If the aminyl, TEMP•, is formed during HALS activation it is most likely to be converted to the nitroxide by reaction 22.[129]

$$TEMP^{\bullet} + ROO^{\bullet} \rightarrow TEMPO + RO^{\bullet} \quad (22)$$

In the case of *N*-methyl-HALS, the initial $TEMPCH_2^{\bullet}$ is probably converted into TEMPO via reactions 23, 24, 25, and 22. Evidence favoring this sequence of reactions has been provided by several reports of formation of $TEMPH_2^{+}$–formate salts in oxidations inhibited by *N*-methyl-HALS.[131,137,138] Formate (formic acid) will, of course, be formed by oxidation of the formaldehyde, reaction 26, which is produced by the β-scission reaction 25.

$$TEMPCH_2^{\bullet} + O_2 \rightarrow TEMPCH_2OO^{\bullet} \quad (23)$$

$$TEMPCH_2OO^{\bullet} + ROO^{\bullet} \rightarrow TEMPCH_2O^{\bullet} + O_2 + RO^{\bullet} \quad (24)$$

$$TEMPCH_2O^{\bullet} \rightarrow TEMP^{\bullet} + CH_2O \quad (25)$$

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$$ROO^{\bullet} + CH_2O \rightarrow \rightarrow HCO_2H \quad (26)$$

Nowadays most HALS are alkoxyamines, TEMPOR. In principle, this facilitates formation of the nitroxide by photolysis or thermolysis of the NO−R bond. This process is favored by ca. 3 kcal/mol for most typical polymer-derived R groups over N−OR bond cleavage,[129,139] which contrasts with alkoxyl−diarylamines for which the NO−R and N−OR bond strengths are similar and it is N−OR bond scission that initiates the nitroxide regeneration cycle in diarylamine-inhibited autoxidations,[119] see reactions 13−17 above.

4.1.2. Mechanism of Catalytic Inhibition by HALS at Ambient Temperatures. It is obvious that the (stronger) N−OR bond in the TEMPOR species formed during the polymer's oxidative degradation must be cleaved during HALS inhibition if we are to account for the observed high stoichiometric factors[118,127] and formation, presumably from $TEMP^{\bullet}$, of TEMPH.[134−136] Surprisingly, the obviously facile abstraction of the H-atom from the TEMPOR moiety, N−O−C*H*, by $ROO^{\bullet}$, reaction 27, had been overlooked despite the well-known propensity of diethyl ether and diisopropyl ether to undergo ambient temperature autoxidation (giving explosive peroxides).

$$ROO^{\bullet} + TEMPOCHRR' \rightarrow ROOH + [TEMPOC^{\bullet}(R)(R')] \quad (27)$$

$$[TEMPOC^{\bullet}(R)(R')] \rightarrow TEMP^{\bullet} + C(O)RR' \quad (28)$$

Reaction 27 will be facilitated by the aforementioned tendencies of polymers to concentrate "impurities" in microdomains. Reaction 28 is strongly exothermic (by 26−44 kcal/mol depending on structure)[129] and will be essentially "instantaneous".

Once reactions 27 and 28 had been postulated as the simplest explanation for the high *n* values for HALS in polymers, they quickly received support from theory.[129] These two reactions were also supported by earlier experimental results.[133−135] Theoretical calculations using several R groups, chosen to serve as models for radicals derived from different polymers (e. g., PhCHMe for polystyrene),[129] showed that reaction 27 is both thermodynamically and kinetically competent to participate in $TEMPO^{\bullet}$ recycling in HALS-protected polymers via reactions 27, 28, and 22. The aminyl radical, $TEMP^{\bullet}$, produced in reaction 28 serves both as a source of $TEMPO^{\bullet}$ (reaction 22, direct recycling) and as a source of amine, TEMPH (reaction 29).

$$TEMP^{\bullet} + XH \rightarrow TEMPH + X^{\bullet} \quad (29)$$

In reaction 29, XH represents some H-atom donor present in the microdomain where this chemistry is proceeding, most probably ROOH.[129,136] Reaction 29 "stores" the TEMP moiety until it is "reactivated" by loss of the amino H-atom, reaction 20.

This $TEMPO^{\bullet}$ recycling mechanism is consistent with formation of TEMPH during the oxidative degradation of HALS-protected polymers.[135,136] It is also consistent with the report[134] that TEMPH is formed during the thermal decomposition of TEMPOR *provided* R is a secondary alkyl group, CHRR′. TEMPH was not produced when R was a tertiary alkyl group.[134]

The $TEMPO^{\bullet}$ recycling mechanism of reactions 27, 28, and 22 also explains the results of (misinterpreted) isotopic-labeling experiments using *N*-(cyclohexyloxyl)-2,2,6,6-tetramethylpiperidinyl benzoate in oxidizing cyclohexane at 60 °C.[133] In this work, it was unequivocally demonstrated that the cyclohexanone derived from the alkoxyamine acquired its oxygen *exclusively* from the alkoxyamine (consistent with reactions 27 and 28) and that the nitroxide that was formed acquired its oxygen *exclusively* from the $^{18}O^{18}O$ gas (consistent with reaction 22).

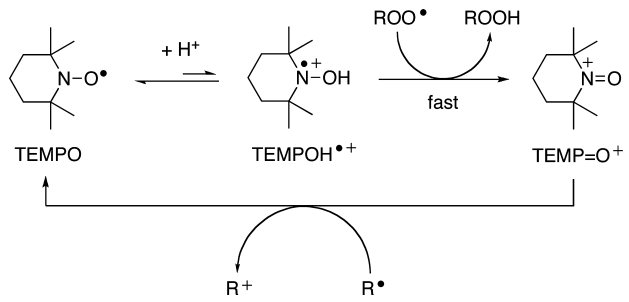
Proper mechanistic understanding can lead to improved product yields and enhanced reaction rates. This is not true, unfortunately, in the present case because the rate-determining step for $TEMPO^{\bullet}$ recycling (reaction 27) depends on the polymer, not on the active $TEMPO^{\bullet}$ portion of the HALS. Thus, although HALS with some improved properties may be discovered, it seems unlikely that higher *n* values will be achieved while using TEMPO-based HALS.

4.2. Effect of Organic Acids on the RTA Activity of TEMPO

The preceding section is not the end of the story about TEMPO recycling at ambient temperatures. In 2010, it was reported[36] that in the AIBN-initiated autoxidations of cumene or styrene TEMPO induced an "apparently infinite" inhibition period in the presence of acetic or benzoic acids. This means that these two weak organic acids cause an enormous enhancement in the stoichiometric factor, *n*, of TEMPO. In the absence of these two acids the *n* value for TEMPO is 1, corresponding to its capture of one carbon-centered radical per TEMPO.[120] Under normal conditions this nitroxide does not react with peroxyl radicals.[120] Surprisingly, *n* was also 1 in the presence of strong acids such as dichloroacetic, trifluoroacetic, and *p*-toluenesulfonic acids.[36] These strong acids protonate the nitroxide to give radical cations that were calculated to have O−H BDEs that were ca. 10 kcal/mol weaker than the neutral hydroxylamine.[36] Not surprisingly, therefore, the radical cation, $TEMPOH^{\bullet+}$, formed by addition of *p*-toluenesulfonic acid (PTSA), was found to react very rapidly with $ROO^{\bullet}$, e.g., $k = 1.4 \times 10^8\ M^{-1}\ s^{-1}$ in the presence of 100 mM PTSA.[36]

It was proposed[36] that the first step in the weak carboxylic acid-induced extreme *n* values was oxidation of $TEMPOH^{\bullet+}$ by $ROO^{\bullet}$ to form the oxoammonium ion (Scheme 8), but how

Scheme 8. Proposed Mechanism for the Acid-Catalyzed RTA Activity of TEMPO



this might be reduced to reform the nitroxide was not addressed. Consideration of all the species present in a TEMPO/$MeCO_2H$ inhibited autoxidation leaves only one possible candidate to reduce the $TEMP{=}O^{+}$: the alkyl radical, $R^{\bullet}$.[140]

This reaction has been suggested as a step in the catalytic cycle proposed by Baran for guided unsaturation of unactivated aliphatics,[182] and has been subsequently shown by us to be quite facile.[141] Cumyl radicals were generated by thermal decomposition of azocumene at 50 °C in acetonitrile containing an equivalent of the acetate salt of $TEMP{=}O^{+}$

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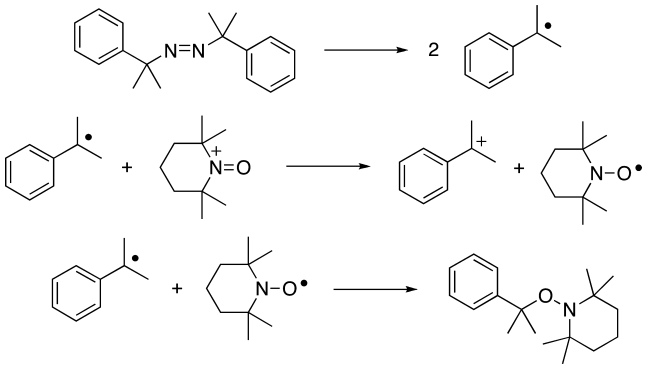
(1:1) to yield the alkoxyamine derived from the coupling of TEMPO with the second equivalent of cumyl radicals (Scheme 9).

Scheme 9. Preliminary Evidence for the Reduction of the TEMPO-Derived Oxoammonium Ion by Alkyl Radicals



Although preliminary, this data strongly supports addition of the reactions in Scheme 8 to the other mechanisms for recycling TEMPO• during autoxidations that were discussed above. This recycling scheme might play a role in many TEMPO• (HALS) inhibited autoxidations since carboxylic acids are (surprisingly) one of the initial products formed (together with methyl ketones) during the autoxidation of paraffins at elevated temperatures.[142−144] However, these simple recycling reactions certainly cannot dominate recycling in HALS inhibited oxidations because this new cycle does not produce the aminyl radical, TEMP•. It is this aminyl radical that must be the source of the observed amine, TEMPH, and in the presence of $^{36}O_2$ the source of TEMP^{18}O•, see previous section.[133]

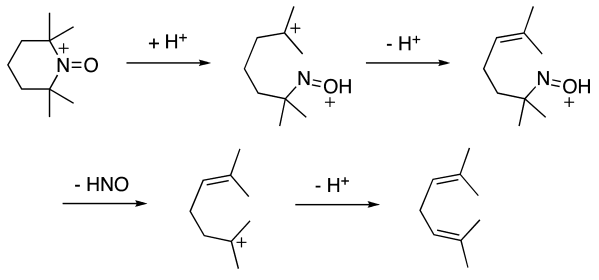
This still leaves one problem: Why are high n values found for TEMPO• in the presence of weak acids, such as acetic acid, but not strong acids, such as trifluoroacetic acid? The most likely answer seems to be that the TEMP=O$^+$ oxoammonium ion decomposes in strong acids.[145] One decomposition route, shown in Scheme 10, is supported by the observed formation of N_2O which could arise from condensation of two molecules of HNO.

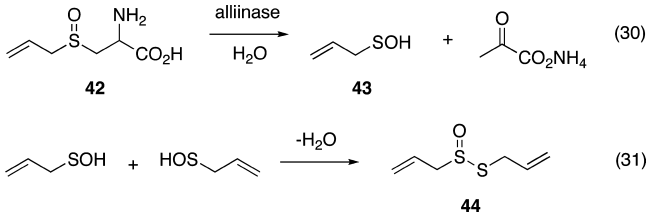
5. SULFENIC ACID RTAs

5.1. Organosulfur Compounds from Garlic and Other Alliums

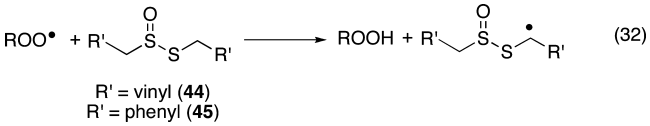
Garlic, onion, and other plants of the *Allium* species, long believed to have medicinal properties, contain up to 5% dry weight of nonproteinogenic sulfur amino acid secondary metabolites.[146,147] For example, garlic contains (+)-*S*-allyl-L-cysteine *S*-oxide (alliin, **42**), which is converted to ammonium pyruvate and 2-propenesulfenic acid (**43**) by the pyridoxal-dependent C−S lyase alliinase, upon crushing or cutting the clove, reaction 30. This sulfenic acid then undergoes a self-condensation to give diallyl thiosulfinate, allicin (**44**), reaction 31.

Scheme 10. Decomposition of the TEMPO-Derived Oxoammonium Ion in Strong Acids[145]





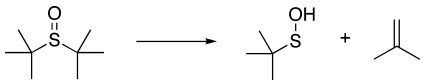
It is allicin that provides garlic with its odor and flavor. Allicin is also believed to be responsible for garlic's (putative) health benefits, which are often ascribed to its antioxidant activity. Kinetic studies by Okada et al.[148,149] demonstrated that allicin had RTA activity in the initiated autoxidation of methyl linoleate and cumene. Since the S(O)SCH$_2$CH=CH$_2$ group was found to be essential for RTA activity, Okada et al. proposed that the peroxyl radicals abstracted the allylic H-atom adjacent to the divalent sulfur atom, reaction 32, and provided estimates for k_{32} of ca. 10^3 and 10^5 M^{-1} s^{-1} in methyl linoleate and cumene, respectively. Similar results were obtained with dibenzyl thiosulfinate, PhCH$_2$S(O)SCH$_2$Ph (petivericin, from *Petiveria alliacae* L.) and were attributed to abstraction of a benzylic H-atom by ROO•.[150]



Not only are RTA activities due to H-atom abstraction from CH groups by ROO• as rare as hens' teeth, but also the k_{32} values reported were impossibly large for such H-atom abstractions and differed by an unprecedented 2 orders of magnitude between a secondary and a tertiary alkylperoxyl. These anomalies attracted attention, and the mechanism proposed by Okada et al. was quickly shown to be incorrect. Amorati and Pedulli[151] demonstrated that diallyl disulfide did not inhibit the azo-initiated autoxidation of cumene or styrene and estimated a rate constant for ROO• abstraction of an allylic H-atom next to an S−S bond of only ca. 1.6 M^{-1} s^{-1}. At the same time, one of us recalled that in 1972 Koelewijn and Berger[152] demonstrated that di-*tert*-butyl sulfoxide was an effective inhibitor of hydrocarbon autoxidations at 60 °C because it decomposed by a Cope elimination to form *tert*-butyl sulfenic acid and isobutylene, reaction 33. Furthermore, these workers estimated that the rate constant for reaction of this sulfenic acid with ROO• was greater than 10^7 M^{-1} s^{-1}, making *t*-BuSOH one of the most potent ROO• trapping agents.

Thiosulfinates undergo Cope eliminations even more readily than sulfoxides because the S−S bond in a thiosulfinate is weaker than the C−S bond in a sulfoxide. These reactions do not require elevated temperatures and yield sulfenic acids and thioaldehydes or thioketones. They are particularly facile for allyl and benzyl thiosulfinates because only relatively weak C−H bonds have to be broken. In fact, allicin, **44**, was known to

dx.doi.org/10.1021/cr500226n | Chem. Rev. 2014, 114, 9022−9046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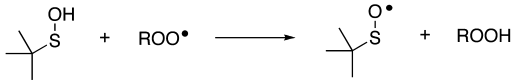
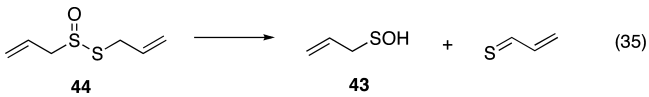

(34)

undergo Cope elimination at room temperature to (re)form 2-propenesulfenic acid, **43**, and thioacrolein, reaction 35. These "known" facts strongly suggested that **43** was responsible for the RTA activity of **44** and that phenylmethanesulfenic acid, **46**, was responsible for the antioxidant properties of petivericin (**45**), reaction 38. Preliminary experiments and calculations supported this suggestion.[37]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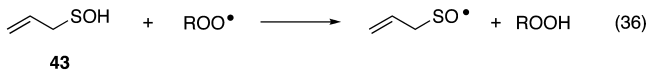
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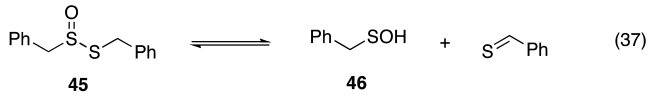
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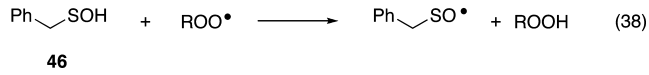
(38)

Allyl and benzyl sulfenic acids cannot be isolated for controlled studies of their RTA activities because of their rapid self-condensation reactions, e.g., reaction 31. Therefore, the initial investigation focused on indirect methods to show that the sulfenic acid decomposition products were likely responsible for the RTA activities of thiosulfinates.[37] It was already well established that hydrogen-bond donor (HBD) solvents retard the decomposition of allicin,[146] **44**, and at 37 °C, the half-life for **44** (50 μM) in chlorobenzene was found to be ca. 1 h, but when the strong HBD, $(CF_3)_2CHOH$ (0.15 M), was present very little **44** decomposed. More importantly, the (50 μM) allicin-induced induction period of ca. 40 min in an AIBN-initiated autoxidation of methyl linoleate in chlorobenzene at 37 °C was completely eliminated by addition of 0.15 mM $(CF_3)_2CHOH$. Such a dramatic result could not arise if H-atom abstraction from a CH_2 group in allicin was responsible for the RTA activity of allicin.[37] This RTA reaction most likely involves an H-atom abstraction from an OH group, and this implies that there should be another kinetic solvent effect since hydrogen-bond acceptor (HBA) solvents greatly reduce ArOH RTA activities by H bonding to the reactive H-atom.[51,52] Addition of the HBA, CH_3CN (1 M), to a chlorobenzene solution of allicin had little effect on allicin's rate of decomposition at 37 °C but markedly reduced its ability to inhibit the autoxidation of methyl linoleate.[37] This result is consistent with the RTA activity of allicin being due to its decomposition to a sulfenic acid (**43**) which transfers its labile H-atom to ROO$^\bullet$, reaction 36, but not with its donation of an H-atom to ROO$^\bullet$ from a CH_2 group, reaction 32.

Unfortunately, neither the rate constants for peroxyl radical trapping (i.e., the rate constant for inhibition (k_{36} and k_{38}) nor the stoichiometric factors, n, for these reactions could be measured because the concentration of the sulfenic acid could not be determined.[37] This led to theoretical calculations of O−H BDEs in sulfenic acids and to the search for persistent sulfenic acids that would permit experimental measurements both of k_{39} and of R′SO−H BDEs.

$$ROO^\bullet + R'SOH \rightarrow ROOH + R'SO^\bullet \quad (39)$$

Calculations[37] gave R′SO−H BDEs of 68.6 kcal/mol for R′ = $CH_2{=}CHCH_2$ (**43**), $(CH_3)_3C$, and $PhCH_2$ (**46**). Not only are these BDEs roughly 18 kcal/mol weaker than R′OO−H bonds in alkyl hydroperoxides but also they are among the weakest O−H bonds known, comparable to the TEMPO−H BDE of 69.7 kcal/mol.[153] The sulfur atom stabilizes R′SO$^\bullet$ conjugatively, acquiring ca. 50% of the unpaired spin (vs 30% on the inner O-atom of ROO$^\bullet$). With such weak O−H bonds it is not surprising that sulfenic acids are outstanding RTAs, an activity greatly aided by their acidity and therefore their ability to form a strong HB to a peroxyl radical. These calculations revealed that the H-bonded prereaction complex for reaction 36 lies lower in energy (by some 4.5−5.0 kcal/mol) than the separated reactants and that the transition state is also lower in energy than the reactants. The RTA reactions of sulfenic acids were therefore predicted to be diffusion controlled.[37] The calculations also indicated that a syn transition state was favored for H-atom abstraction from sulfenic acids by peroxyl radicals.[37]

Preliminary work on 2-propenesulfenic acid, **43**, was confirmed and extended to phenylmethanesulfenic acid, **46**.[154] An interesting difference in the (apparent) stabilities of their thiosulfinate precursors made it at first appear that the sulfenic acid theory for their RTA activities must be incorrect. Thus, allicin, **44**, decomposed steadily in chlorobenzene via a Cope elimination to form **43** and thioacrolein, reaction 35. This process is essentially irreversible because thioacrolein is highly reactive and can undergo various reactions, including a self (bimolecular) [4+2] cycloaddition. In contrast, dibenzyl thiosulfinate appeared to be stable under the same conditions! However, this was shown to be due to the reversibility of reaction 37 by adding the good electrophile, ethyl propiolate, to capture the nucleophilic phenylmethanesulfenic acid. In the presence of propiolate, the rate of decomposition of the dibenzyl thiosulfinate scarcely differed from that of allicin.[154] Clearly, thiobenzaldehyde is much less reactive than thioacrolein. Later,[155] $PhCD_2S(O)SCD_2Ph$ and propiolate were used to determine deuterium kinetic isotope effects (DKIE) of 4.5 for the Cope elimination (reaction 37) and, using peroxyl radical clock methodology, an overall DKIE of 18.2 for the apparent reaction of petivericin with peroxyl radicals. Although the unknown concentrations of sulfenic acid present during the thiosulfinate inhibited autoxidations prevented determination of the inhibition rate constants, k_{36} and k_{38} inhibited autoxidation and peroxyl radical clock experiments left no doubt that sulfenic acids were outstanding peroxyl radical traps.[37,154]

Synthesis of a persistent sulfenic acid was undertaken in order to properly measure its RTA properties. An added incentive was that sulfenic acid instabilities meant that there is very little information about their fundamental physicochemical properties despite the fact that they feature prominently in biology, e.g., cysteine-derived sulfenic acids are key intermediates in signal transduction, responding to the cell's redox state and modulating gene transcription accordingly.[156] Very few persistent sulfenic acids have been prepared, the rapid self-condensation being overcome either by intramolecular H-bonding or by classic employment of steric effects to protect

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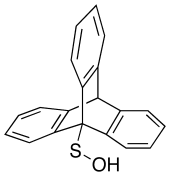
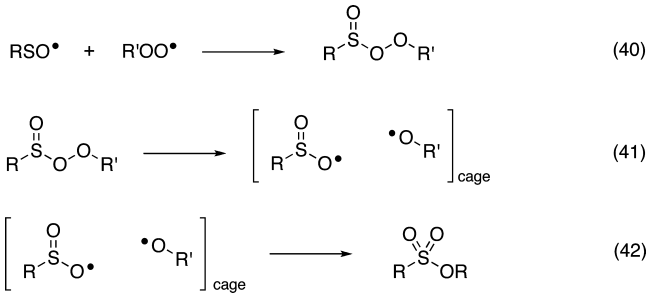
the reactive center. The latter approach appeared to better mimic the sulfenic acids of interest, though it was obvious that steric hindrance would make the SOH moiety somewhat less reactive than it is in **43** and **46**. A practical synthesis of 9-triptycenesulfenic acid, **47**,[157] was developed.[158]



47

Hydrogen atom abstraction from **47** gave a persistent sulfinyl radical that was unreactive toward O_2. Application of the ESR equilibrium method using photolysis of a benzene solution of di-*tert*-butyl peroxide, **47**, and TEMPOH (O−H BDE = 69.6 kcal/mol) gave the O−H BDE in **47** as 71.9 kcal/mol,[158] in good agreement with the earlier calculations.[37] The pK_a of **47** and oxidation potential of the sulfinyl radical/sulfenate anion couple were also reported.[158] Compound **47** inhibited autoxidation of styrene at 30 °C with k_{39} = 30 × 10^5 M^{-1} s^{-1} in chlorobenzene, which is the same as for the best of Nature's RTAs, α-T, under these conditions.[155] This reaction showed (as expected for an acidic H-atom donor RTA) a substantial kinetic HBA solvent effect, k_{39} = 1.6 × 10^5 M^{-1} s^{-1}, in acetonitrile with $k_{39}{}^{H}/k_{39}{}^{D}$ = 6.1 in this solvent.[155] Surprisingly, the stoichiometric factor was only 0.25−0.4. Theory suggested[154] that the fast cross-coupling of sulfinyl and peroxyl radicals[155] gave an initial peroxysulfinate (reaction 40) that underwent O−O bond cleavage (reaction 41). The resultant radical pair either recombined in cage to give a sulfonate ester (reaction 42) or escaped the cage and continued the autoxidation chain. This chemistry provides a neat explanation for the observed[155] low stoichiometric factors when **44** was used as an RTA. The rate constants for ROO• trapping by the



(40)

(41)

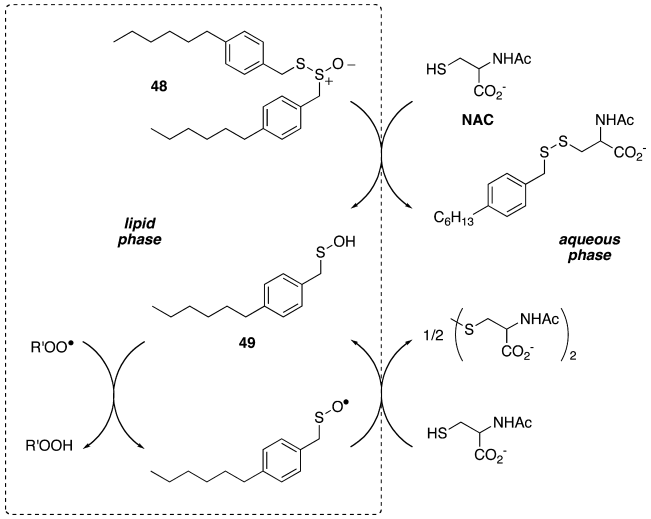
(42)

persistent sulfenic acid **47** and α-T (**2**) are virtually identical (30 × 10^5 M^{-1} s^{-1})[155] despite the fact that the sulfenic acid's O−H BDE is ca. 5 kcal/mol weaker than that of α-T. Clearly the steric protection of the SOH group that makes the sulfenic acid (and its radical) persistent also retards H-atom transfer to ROO•. Indeed, kinetic simulations of petivericin-inhibited autoxidations enabled estimation of the rate constant for the unhindered phenylmethanesulfenic acid of 280 × 10^5 M^{-1} s^{-1}, 10 times larger than that of **47** (and α-T).[155]

Finally, though certainly not the "last word" on the RTA properties of thiosulfinates (indirect) and sulfenic acids (direct), it has been found that a lipophilic sulfenic acid is an outstanding RTA for inhibiting autoxidation of (biomimetic) phosphatidylcholine bilayers in aqueous dispersion *provided* a water-soluble thiol is also present.[159] This result is reminiscent of the well-known "regeneration" of lipid-soluble vitamin E (α-T) by water-soluble vitamin C (ascorbate) in a similar system,[109] a process that is generally believed to be relevant in controlling oxidative stress in vivo. Since water-soluble thiols, such as glutathione, are present in mammalian cells in millimolar concentrations but do not "regenerate" α-T in these model systems, it is quite possible that "regeneration" of lipid-soluble/protein-bound sulfenic acids by aqueous thiols plays just as important a role in controlling in vivo oxidative stress as the interactions of vitamins E and C.

Autoxidation of aqueous dispersions of phospholipid bilayers was not noticeably retarded by addition of allicin (**44**), petivericin (**45**), or its lipophilic analog di(4-hexyltolyl)-thiosulfinate (**48**).[159] However, because sulfenic acids were known[146] to be formed by reactions of thiosulfinates with nucleophiles, such as thiols, these experiments were repeated in the presence of water-soluble *N*-acetylcysteine (NAC). By itself, the *N*-acetylcysteine did not retard bilayer autoxidation nor did it retard oxidation of the bilayers containing allicin or petivericin. However, with the much more lipophilic dihexyltolylthiosulfinate in the bilayer, there was very strong inhibition of autoxidation, together with unequivocal proof that the active RTA in this system, i.e., the sulfenic acid **49**, was being "regenerated". The chemistry is shown in Scheme 11. It

Scheme 11. Lipophilic Petivericin Analog 48 Is an Excellent RTA in Lipid Bilayers in the Presence of Thiols Owing to Formation of the Lipophilic Sulfenic Acid 49 by S-Thiolation and Regeneration of the Sulfinyl Radical Following Radical Trapping



would appear that the 2-propene and phenylmethanesulfenic sulfenic acids derived from allicin and petivericin are too water soluble and are simply consumed by reactions with NAC, giving mixed disulfides, whereas the more lipophilic sulfenic acid derived from **48** is sufficiently lipophilic to remain in the bilayer.

Interestingly, recent studies in mammalian cells reveal that allicin and petivericin can inhibit oxidation of membrane lipids, but at concentrations only marginally higher they are cytotoxic.[141] Taken with the results in liposomes,[159] these results suggests that plant-derived thiosulfinates are not RTAs in vivo and imply that their mechanisms of action are instead

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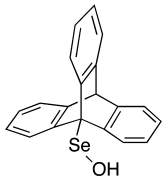
glutathione depletion and/or reaction with nucleophilic cysteines on signaling proteins that regulate transcription of antioxidant genes. In contrast, the hexylated petivercin **48** inhibits lipid peroxidation in cells, as it did in liposomes, but is not cytotoxic. These results suggest that lipophilic thiosulfinates, such as **48**, operate by a different mechanism and could be effective RTAs in both organic solution and cells.

5.2. Insights from Reactions of Selenenic Acids

The now known fact that sulfenic acids have O−H BDEs which are ca. 14 kcal/mol lower than their (valence) isoelectronic cousins, the hydroperoxides, naturally prompts the fundamental question: would the O−H bond in a selenenic acid follow the periodic trend and be even weaker? Considerations of relevance aside, academic curiosity encouraged one of us to follow up our work with the 9-triptycenesulfenic acid **47** with the synthesis and study of the corresponding selenium analog, 9-triptyceneselenenic acid, **50**.[40]



50

In fact, the O−H BDE of **50**, measured using the radical equilibration technique, was 81 kcal/mol; therefore, 9 kcal/mol *stronger* than that in **47** (72 kcal/mol)[158] and actually more similar to the O−H BDE in an alkylhydroperoxide (86 kcal/mol). It was surmised that the longer Se−O bond in the selenenyl radical, when compared to the S−O bond in the sulfinyl radical, leads to less delocalization of the unpaired electron onto the chalcogen atom and a correspondingly higher O−H BDE.[40]

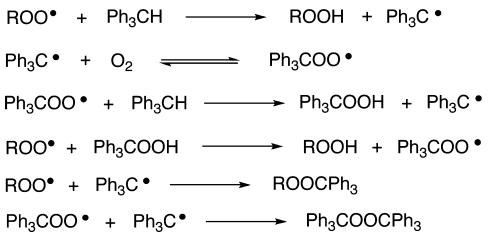
The RTA activity of **50** was determined by the conventional[12] inhibited autoxidation of styrene approach. The inhibition rate constant for **50** was found to be 1.7×10^5 M^{-1} s^{-1}, just over an order of magnitude lower than that determined the same way for **47** (30×10^5 M^{-1} s^{-1}),[40] a surprising result given that reaction of **50** with peroxyls was 9 kcal/mol less exothermic. Kinetic isotope effects and kinetic solvent effects supported the same mechanism for reactions of **50** and **47** with peroxyl radicals, as did computation, which predicted that syn TS structures typical of phenol + peroxyl reactions would lead to rate constant differences consistent with the experimental observations.[40]

The importance of the interactions of the orbitals centered on the chalcogen atom and the inner oxygen atom of the peroxyl leading to the syn TS structures were probed in reactions of smaller, unhindered sulfenic and selenenic acids with peroxyl radicals, i.e., *t*-BuSeOH + $^{\bullet}$OOMe and *t*-BuSOH + $^{\bullet}$OOMe. These calculations, at the same level of theory which correctly predicted that **47** would react just over an order of magnitude faster with peroxyl radicals than **50**, predicted that *t*-BuSeOH would be more reactive than *t*-BuSOH! Careful consideration of these TS structures revealed that better overlap could be achieved between the chalcogen atom and the inner atom of the peroxyl radical in the smaller, unhindered selenenic/sulfenic acids, and since the selenium atom's lone pair is higher in energy than the sulfur atom's, this interaction is better for the selenenic acid than for the sulfenic acid, driving the barrier lower for the former than for the latter.[40] Studies of selenenic acids, while unlikely to offer any practical use, have provided the most compelling evidence to date for a role of secondary orbital interactions in H-atom transfer reactions.

6. CARBON-CENTERED RADICALS AS RTAs

Addition of molecular oxygen (a triplet diradical in its ground electronic state) to the vast majority of carbon-centered radicals (doublets), reaction 2, occurs at the diffusion-controlled limit (corrected for spin selection for a triplet/doublet pair).[1] For most substrates, reaction 2 is essentially irreversible at the temperatures commonly encountered by oils and polymers (ca. 0−160 °C). However, if R$^{\bullet}$ is strongly resonance stabilized, reaction 2 can be reversible at ambient temperatures and, as a consequence, the uninhibited autoxidation chain is terminated by the (fast) R$^{\bullet}$ + ROO$^{\bullet}$ cross-reaction, eq 5. This means that the autoxidation of a hydrocarbon, RH, that yields a resonance-stabilized R$^{\bullet}$ is self-retarded, with self-retardation becoming more pronounced as the O_2 partial pressure is reduced and/or the temperature is increased. Such hydrocarbons can also function as RTAs toward other organic substrates, since their resonance-stabilized R$^{\bullet}$ will efficiently trap the peroxyl radicals derived from the substrate. For example, the highly stabilized trityl radical, $Ph_3C^{\bullet}$, makes triphenylmethane, Ph_3CH, an effective retarder of the autoxidation of cumene[160,161] and cyclohexene.[161] More interestingly, trityl hydroperoxide, Ph_3COOH, also retards the autoxidation of cumene, tetralin, and 9,10-dihydroanthracene.[162] In all these systems, retardation of substrate autoxidation becomes more pronounced when the oxygen partial pressure is reduced or the temperature is increased. These results are readily accommodated by the reactions shown in Scheme 12. Similar chemistry explains why the conjugated polyene, *β*-carotene, retards the oxidation of tetralin and methyl linoleate.[163]

Scheme 12. Relevant Reactions in the Retardation of Hydrocarbon Autoxidation by Triphenylmethane and Its Hydroperoxide



The RTA activities of Ph_3CH, Ph_3COOH, and similar compounds are little more than academic "curiosities". However, a mechanistically related group of RTAs has achieved industrial importance. This story begins with CIBA's claim[164] that *Irganox HP-136* (HP-136) provided long-term protection of polymers against oxidative degredation and was an excellent antioxidant for high-temperature polymer processing. This astonishing claim caught the attention of one of the present authors because HP-136 contained no known antioxidant functionality. Intrigued by what was obviously "new" chemistry, Scaiano and co-workers undertook thoughtful and extensive studies on the properties of HP-136, its radical HP-136$^{\bullet}$, the head-to-head radical dimer $(HP\text{-}136)_2$, and related compounds.[165−175]

As pointed out earlier, RTAs rarely act by H-atom donation from C−H bonds to ROO$^{\bullet}$, yet the benzylic C−H in HP-136

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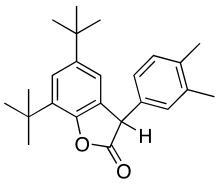
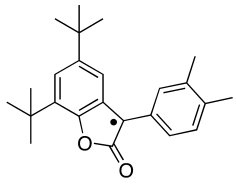

HP-136


HP-136•

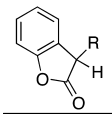
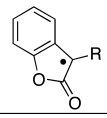
(which is essential for antioxidancy)[164] would appear, *at first glance*, to be the only possible site of H-atom donation. The resultant HP-136• is very similar in structure to the diphenylmethyl radical, $Ph_2CH^•$. These two radicals were generated by H-atom abstraction from their parents by alkoxyl radicals formed from di-*tert*-butyl peroxide and dicumyl peroxide by laser flash photolysis, LFP.[165] (Alkoxyl radicals are much more reactive than peroxyls in H-atom abstractions.) The resultant HP-136• and $Ph_2CH^•$ have virtually identical UV absorption bands.[165] However, these two radicals behaved very differently in the presence of O_2. The $Ph_2CH^•$ radical's signal was totally quenched, whereas O_2 did not produce any appreciable changes in the very slow rate of decay of the HP-136• radical. The rate constant for reaction of the HP-136• radical with O_2 was estimated to be $<10^5$ M^{-1} s^{-1}, which is nearly 5 orders of magnitude less than the rate constant for the $Ph_2CH^•$ + O_2 reaction (6.3×10^8 M^{-1} s^{-1}).[176] It was assumed that the HP-136• radical must react with O_2 but that this reaction is reversible and favors the carbon-centered radical to about a 1000-fold greater extent than is the case for the $Ph_3C^•$/$Ph_3COO^•$ couple.[165] Peroxyl radical trapping by the HP-136• radical seems likely to play a major role in making HP-136 an effective antioxidant at the high temperatures of polymer processing.

Follow-up LFP studies[166] showed that a number of 2-coumaranone-derived radicals that were structurally less complex than HP-136• were also unreactive toward O_2, see Table 3. Five possible reasons[177] for the lack of reactivity toward O_2 of these radicals were proposed[166] and later explored experimentally.[167−169] Since this work is only of peripheral interest to the present review, it will not be described further. Moreover, theory has provided a simple and elegant explanation for the low reactivity of these and other carbon-centered radicals toward oxygen,[178,179] that is, calculations of the C−OO• bond dissociation enthalpies of substituted methylperoxyl radicals ($YCH_2OO^•$) revealed that C−OO• bond strengths were not governed solely by the stability of the $YCH_2^•$ radical but were strongly affected by hyperconjugation when Y is electron-donating or conjugating.[178] In many cases, the hyperconjugating effects were greater than stabilization of the methyl radical by the Y group. It was also found that all electron-withdrawing Y weakened the $YCH_2OO^•$ bond by inductive electron withdrawal from the polarized C−OO• bond.[178] The simplest HP-136 analogue, i.e., the final compound, R = H, shown in Table 3, did not react with oxygen.[166] Calculations using an even simpler model in which the aromatic ring in this compound was replaced by a simple double bond gave the C−H BDE = 78.9 kcal/mol and the C−OO• BDE = 5.7 kcal/mol with ΔG for O_2 loss from this peroxyl = −5.1 kcal/mol.[178] For comparison, these calculations also gave the allylic C−H BDE in $CH_2{=}CHCH(-H)CH_3$ as 85.9 kcal/mol and C−O BDE in $CH_2{=}CHCH(-OO^•)CH_3$ as 22.0 kcal/mol with ΔG for O_2 loss = 10.6 kcal/mol. In short, theory and experiment agree that olefins can readily autoxidize whereas HP-136 and its analogues cannot.

Interestingly, H-atom abstraction by *tert*-butoxyl from HP-136 and simpler 2-coumaranones in benzene at room temperature was faster by 1−2 orders of magnitude than H-atom abstraction from diphenylmethane,[166] see Table 3. This result provides a strong clue about the true source of the abstracted H-atom. Recall that O-atom-centered radicals abstract H-atoms from O−H donor groups very much more rapidly than from a C−H donor of comparable bond strength, largely because of prior H-bond formation between the reactants and H-atom transfer by the PCET mechanism, see above. This made it probable that H-atom abstraction from HP-136 and its analogues by *tert*-butoxyl (and ROO•) occurred primarily from the enol, even at small enol/ketone ratios, see Scheme 13.

Evidence strongly favoring H-atom abstraction from the enol form of these compounds was obtained 4 years later by studying the effect of solvents on the rate constants for H-atom abstraction from HP-136 by the *tert*-butoxyl radical and a nitroxide.[171,175] As mentioned earlier, the rate constants for H-atom abstraction from phenols and other H-bond donor (HBD) OH-containing compounds are considerably slower in H-bond-accepting (HBA) solvents because HB formation provides steric protection to the OH group against an attacking radical.[51,52] Since CH groups are generally not HBDs (a few are very weak HBDs) solvent effects on H-atom abstraction from CH groups are generally nonexistent (or very minor). Consistent with H-atom donation from the HP-136 enol, changing the solvent from hexane to acetonitrile caused the *tert*-butoxyl and nitroxide rate constants (which differ by 7 orders of magnitude in *n*-octane) to decrease by factors of ∼12 and ∼35, respectively. Moreover, a plot of the *tert*-butoxyl rate constants for H-atom abstraction from HP-136 in six solvents with different HBA activities[180] was linear.[171,175] The keto/enol equilibrium shown in Scheme 13 implies that the benzylic H-atom in HP-136 should exchange with deuterium in the presence of D_2O. This was shown (NMR) to occur, the half-life for CH/CD exchange being a bit under 2 min, with 90% exchange occurring after 5−6 min. However, under the same conditions the LFP kinetic measurements showed that 90% of

Table 3. Rate Constants for the Reactions of Diphenylmethane, HP-136, and Some Related Coumaranones with *tert*-Butoxyl Radicals and the Reactivity of the Product Radicals Toward O_2

Substrate	+ *t*-BuO• $10^{-6}k$ / $M^{-1}s^{-1}$	Radical	Radical reacts with O_2?
Ph_2CH_2	0.91	Ph_2CH•	yes
HP-136	12.4	HP-136•	no
 R = Ph	18.4	 R = Ph	no
R = CH_3	84	R = CH_3	no
R = H	51	R = H	no

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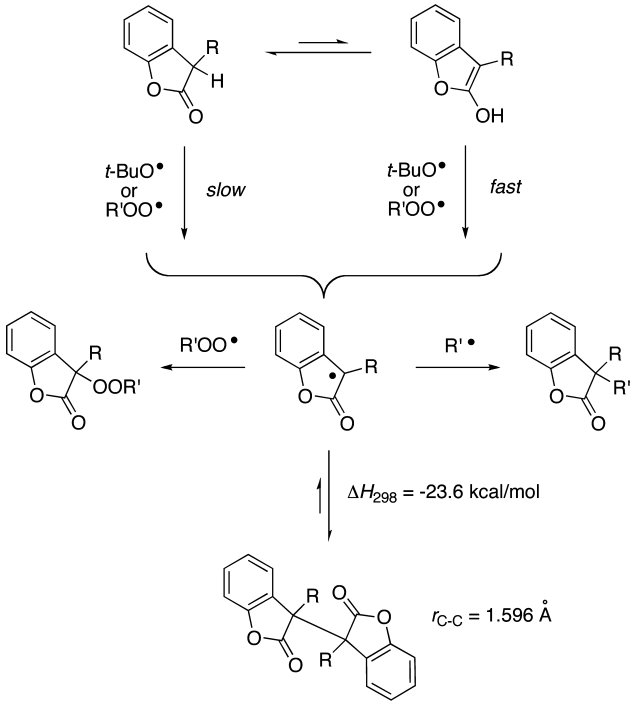
Scheme 13. H-Atom Abstraction from Coumaranones Occurs from Their Enol Tautomers, Producing "Radical" RTAs Whose Fates Are Shown[a]



[a]Note: $(HP\text{-}136)_2$ dimer. ΔH_{298} = −22.8 kcal/mol. Central C−C length = 1.586 Å.

the D_2O-induced decrease in the rate constant occurred in <30 s, implying that the H-atom donor group exchanges H for D much more rapidly than the CH/CD exchange.[171,175] This result is fully consistent with the HP-136 enol being the principal H-atom donor despite its low concentration (estimated [keto]/[enol] = 99.5/0.5 in alkane solvents,[171,175] but a higher fraction of enol is expected in HBA solvents).

The radicals produced by H-atom abstraction from the enol (or keto) form of HP-136 and related compounds (see Scheme 6) may not react with O_2, but they do trap peroxyl- and carbon-centered radicals.[172,173] Such "cross" radical−radical couplings are expected to proceed at rates that approach the diffusion-controlled limit. More significantly, HP-136$^\bullet$ and related radicals also form (meso) "head-to-head" dimers. (In contrast to $Ph_3C^\bullet$, these radicals do not form "head-to-tail" dimers because their radical centers are much less sterically crowded.) Dimerization of the HP-136$^\bullet$ radical (and like radicals) was fully reversible with the radical concentration (monitored by UV) increasing and decreasing as the temperature was raised and lowered.[170] The C−C bonds in these dimers are much longer than is usual for C−C single bonds between sp^3 carbon atoms (e.g., 1.586 Å for $(HP\text{-}136)_2$ vs the typical 1.54 Å), and the C−C BDEs are very low (23−26 kcal/mol),[170] see Scheme 11. Thus, these dimers are in equilibrium with their radicals even at ambient temperatures, e.g., a micromolar solution of the $(HP\text{-}136)_2$ dimer will contain <0.1% of the HP-136$^\bullet$ radical at 30 °C. However, because "cross" radical−radical couplings are extremely fast, even such low steady-state concentrations of HP-136$^\bullet$ ensure that its dimer, $(HP\text{-}136)_2$, is a very effective RTA.[174] For example, $(HP\text{-}136)_2$ completely inhibited the azo-isobutyronitrile (AIBN)-initiated autoxidation of cumene at 30 °C and was a much stronger RTA than HP-136 itself.[174] Using styrene as the oxidizable substrate, the "effective" RTA rate constants for $(HP\text{-}136)_2$ and related dimers were found[174] to be $2-7 \times 10^5$ M^{-1} s^{-1}, values which compare favorably with the most active of the hindered phenols, 2,6-di-*tert*-butyl-4-methoxyphenol (for which $k_7 = 1.1 \times 10^5$ M^{-1} s^{-1})[14] despite the fact that the bulk of these antioxidants must have been present as their non-RTA dimers. The rate constant for the HP-136$^\bullet$ + ROO$^\bullet$ coupling was estimated[174] to be $\sim 1 \times 10^8$ M^{-1} s^{-1}. Note that in contrast to most other RTAs, the antioxidant activity of $(HP\text{-}136)_2$ increases with temperature, e.g., by a factor of 2.4 from 30 to 45 °C, in excellent agreement with the increase in the steady state concentration of HP-136$^\bullet$. These dimers have another feature that may sometimes prove advantageous over RTAs that donate an H-atom to ROO$^\bullet$ from an OH group: they lose none of their effectiveness in HBA solvents.[175]

To end this section, we note that Korth[181] has written an excellent brief review of Scaiano's "radically different antioxidants". Korth does point to a potential "drawback to their practical application", viz., "the long term stability of the radical-dimer systems" particularly toward O_2. Whether this is a problem for the dimers remains to be seen, but it certainly is not a problem for the parent monomer; HP-136 itself, witness current industrial practice.

7. CONCLUSIONS AND OUTLOOK

Many researchers interested in radical oxidation and/or antioxidant chemistry felt there was little more to learn about radical-trapping antioxidants by the turn of the century. The foregoing pages illustrate that nothing could be further from the truth! They also serve to caution us about making predictions about the future of this field or any other. This is particularly true in a biological context—where enthusiasm about the promise of RTAs for degenerative disease prevention has been dampened somewhat in recent years. The reality is that massive investments in time and money (over 2000 hits appear in the U.S. National Institutes of Health clinical trials database associated with the therapeutic and preventive potential of RTAs) have suggested little, if any, role for RTAs in disease pathogenesis. However, upon careful consideration of these studies, two issues immediately come to the fore. First, given the implication of oxidation in the development of disease, it is unlikely that RTAs would ever serve a therapeutic role—a preventive role seems more likely. Second, it is clear *from their chemistry* that the compounds clinicians have tended to study have significant shortcomings as RTAs. For example, α-tocopherol can mediate the peroxidation of lipids, ascorbate can be a prooxidant, and beta-carotene is not a good RTA! Some of the compounds developed since the turn of the century have much greater reactivity than α-tocopherol and could be engineered for similar bioavailability and tissue distribution. Moreover, the fact that they are much less effective at mediating lipid peroxidation could prove useful in addressing the central issue of whether RTAs play a role in keeping degenerative diseases at bay.

At a mechanistic level, many nagging questions about RTAs remain unanswered—even among the most studied group of compounds. For example, (1) does SPLET occur between phenols and alkylperoxyl radicals? Unfortunately, there are no convenient methods for determining the kinetics of these reactions in ionizing media (water, alcohols) wherein they may be expected to take place. These issues need to be addressed. (2) What is the mechanism of catalytic regeneration of

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diarylamines? While the cycle proposed by Korcek is eminently reasonable when there is a very large concentration of diarylamine-derived nitroxide present to compete with O_2 for alkyl radicals, a different mechanism must operate at lower concentrations of diarylamine (nitroxide). The new di(hetero)-arylamines provide an expanded structural toolbox with which structure−activity relationships can be built to help clarify the picture. (3) Related to the preceding question: How important is the recently discovered acid-catalyzed increase in the reactivity of nitroxides? Could this play a role in the apparent catalytic activity of diarylamines? (4) Can medicinal plant-derived organosulfur compounds be RTAs in vivo? Investigations to date reveal that despite the fact that allicin and petivericin are good RTAs in organic solutions, their reactions as electrophiles dominate in cells. What about the other unique organosulfur compounds found in these plants, among them trisulfides and trisulfane-*S*-oxides? For that matter, how many of the natural products purported to be effective RTAs based on "titrations" of their reducing equivalents are actually RTAs? Are they instead electrophiles or pro-oxidants that induce an enzymatic antioxidant response in the cell? Delineation of these mechanisms will be a lot of work but is required if we are to make sense out of often inconsistent reports of the biological activities of many phytochemicals.

From a commercial perspective, there continues to be significant interest in the development of RTA technology. Much of the industrial research effort has been on optimization of the structures of existing RTAs to provide appropriate physical properties (e.g., volatility, solubility, etc.) and identification of combinations of existing RTAs that achieve optimal performance via the synergistic interactions described above. Unsurprisingly, introduction of new RTA core structures in commercial products has lagged simply because the established industry standards (e.g., hindered phenols, alkylated diphenylamines) are very inexpensive to produce and are "good enough" for many of the applications in which RTAs are used. As such, new compounds must demonstrate significantly improved reactivity with respect to what is currently in use to justify the increased cost to produce them, even if that cost may be reduced eventually. Moreover, even if new compounds, such as the heterocyclic RTAs described above, are much more reactive than the industrial standards, their increased reactivity must translate to the more complex media of industrial products and consumer goods, which generally also contain many other additives. While we are aware of niche uses for some of the newer RTA compounds, their widespread use may not be economically viable. This leaves the door wide open for further innovation. Indeed, there is still much to learn!

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Derek Pratt (born 1976) received his B.Sc. (Hon. Chem.) degree from Carleton University in 1999 and his Ph.D. degree from Vanderbilt University in 2003. After completing postdoctoral work at the University of Illinois at Urbana−Champaign in 2005, he returned to Canada to take up a faculty position at Queen's University. In 2010, he moved to the University of Ottawa, where he is Associate Professor and Canada Research Chair in Free Radical Chemistry.

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REFERENCES

(1) Maillard, B.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 5095.
(2) For a few substrates, such as trialkylamines and 1,4-cyclohexadienes, the initial ROO$^{\bullet}$ rapidly decomposes directly (or indirectly via electron transfer) to form R_{-H} and HOO$^{\bullet}$, see, e.g., refs 3−5. The

radical−radical reaction, $ROO^{\bullet} + ROO^{\bullet} \rightarrow O_2 + ROOH$, occurs at close to the diffusion-controlled limit, and some such additives can behave as RTAs.
(3) von Sonntag, C.; Schuchmann, H.-P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1229.
(4) Foti, M. C.; Ingold, K. U. *J. Agric. Food Chem.* **2003**, *51*, 2758.
(5) Amorati, R.; Foti, M. C.; Valgimigli, L. *J. Agric. Food Chem.* **2013**, *61*, 10835.
(6) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1967**, *45*, 793.
(7) Ingold, K. U. *Chem. Rev.* **1961**, *61*, 563.
(8) Halliwell, B.; Gutteridge, J. *Free Radicals in Biology and Medicine*, 4th ed.; Oxford University Press: Oxford, 2007.
(9) Valgimigli, L.; Pratt, D. A. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; John Wiley & Sons, Ltd.: Chichester, UK, 2012.
(10) Foti, M. C. *J. Pharm. Pharmacol.* **2007**, *59*, 1673.
(11) Foti, M. C.; Amorati, R. *J. Pharm. Pharmacol.* **2010**, *61*, 1435.
(12) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1962**, *40*, 1851.
(13) Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194.
(14) Burton, G. W.; Doba, T.; Gabe, E.; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053.
(15) Mahoney, L. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 547.
(16) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1963**, *41*, 1744.
(17) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.
(18) Pratt, D. A.; DiLabio, G. A.; Mulder, P.; Ingold, K. U. *Acc. Chem. Res.* **2004**, *37*, 334.
(19) Pratt, D. A.; DiLabio, G. A.; Valgimigli, L.; Pedulli, G. F.; Ingold, K. U. *J. Am. Chem. Soc.* **2002**, *124*, 11085.
(20) A deprotonated O−H or N−H group would be an even stronger electron donor and provide greater stabilization of an electron-poor phenoxyl radical. For example, deprotonation of ascorbic acid drops the O−H BDE from 81.0 to 72.2 kcal/mol,[21] and deprotonation of 5-hydroxyuracil promotes a formal H-atom transfer to peroxyl radicals.[22]
(21) Amorati, R.; Pedulli, G. F.; Valgimigli, L. *Org. Biomol. Chem.* **2011**, *9*, 3792.
(22) Amorati, R.; Valgimigli, L.; Pedulli, G. F.; Grabovskiy, S. A.; Kabal'nova, N. N.; Chatgilialoglu, C. *Org. Lett.* **2010**, *12*, 4130.
(23) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1963**, *41*, 2800.
(24) Ingold, K. U.; Burton, G. W.; Foster, D. O.; Zuker, M.; Hughes, L.; Lacelle, S.; Lusztyk, E.; Slaby, M. *FEBS J.* **1986**, *205*, 117.
(25) Ingold, K. U.; Wright, J. S. *J. Chem. Educ.* **2000**, *77*, 1062.
(26) Pratt, D. A.; de Heer, M. I.; Mulder, P.; Ingold, K. U. *J. Am. Chem. Soc.* **2001**, *123*, 5518.
(27) Brownlie, I. T.; Ingold, K. U. *Can. J. Chem.* **1966**, *44*, 861.
(28) Like most localized O-centered radicals, $HO^{\bullet}$ is electrophilic and its rate of H-atom abstraction is influenced by polar factors.
(29) The repulsion of parallel electron spins centered on X and Y at the transition state for H-atom transfer between them (i.e., $[X\uparrow\text{---}H\downarrow\text{---}\uparrow Y]^{\ddagger}$) has also been advanced as a key factor affecting the rates of these reactions.[30−32]
(30) Isborn, C.; Hrovat, D. A.; Borden, W. T.; Mayer, J. M.; Carpenter, B. K. *J. Am. Chem. Soc.* **2005**, *127*, 5794.
(31) Zavitsas, A. A.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **1995**, *117*, 10645.
(32) Zavitsas, A. A.; Melikian, A. A. *J. Am. Chem. Soc.* **1975**, *97*, 2757.
(33) Mayer, J. M.; Hrovat, D. A.; Thomas, J. L.; Borden, W. T. *J. Am. Chem. Soc.* **2002**, *124*, 11142.
(34) DiLabio, G. A.; Ingold, K. U. *J. Am. Chem. Soc.* **2005**, *127*, 6693.
(35) DiLabio, G. A.; Johnson, E. R. *J. Am. Chem. Soc.* **2007**, *129*, 6199.
(36) Valgimigli, L.; Amorati, R.; Petrucci, S.; Pedulli, G. F.; Hu, D.; Hanthorn, J. J.; Pratt, D. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 8348.
(37) Vaidya, V.; Ingold, K. U.; Pratt, D. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 157.
(38) Amorati, R.; Pedulli, G. F.; Pratt, D. A.; Valgimigli, L. *Chem. Commun.* **2010**, *46*, 5139.
(39) Hanthorn, J. J.; Valgimigli, L.; Pratt, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 8306.
(40) Zielinski, Z.; Presseau, N.; Amorati, R.; Valgimigli, L.; Pratt, D. A. *J. Am. Chem. Soc.* **2014**, *136*, 1570.
(41) Hu, D.; Pratt, D. A. *Chem. Commun.* **2010**, *46*, 3711.
(42) Mayer, J. M. *Annu. Rev. Phys. Chem.* **2004**, *55*, 363.
(43) Weinberg, D. R.; Gagliardi, C. J.; Hull, J. F.; Murphy, C. F.; Kent, C. A.; Westlake, B. C.; Paul, A.; Ess, D. H.; McCafferty, D. G.; Meyer, T. J. *Chem. Rev.* **2012**, *112*, 4016.
(44) Pratt, D. A.; DiLabio, G. A.; Brigati, G.; Pedulli, G. F.; Valgimigli, L. *J. Am. Chem. Soc.* **2001**, *123*, 4625.
(45) DiLabio, G. A.; Pratt, D. A.; LoFaro, A. D.; Wright, J. S. *J. Phys. Chem. A* **1999**, *103*, 1653.
(46) DiLabio, G. A.; Pratt, D. A.; Wright, J. S. *Chem. Phys. Lett.* **1999**, *311*, 215.
(47) DiLabio, G. A.; Pratt, D. A.; Wright, J. S. *J. Org. Chem.* **2000**, *65*, 2195.
(48) Wijtmans, M.; Pratt, D. A.; Valgimigli, L.; DiLabio, G. A.; Pedulli, G. F.; Porter, N. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4370.
(49) Wijtmans, M.; Pratt, D. A.; Brinkhorst, J.; Serwa, R.; Valgimigli, L.; Pedulli, G. F.; Porter, N. A. *J. Org. Chem.* **2004**, *69*, 9215.
(50) Valgimigli, L.; Brigati, G.; Pedulli, G. F.; DiLabio, G. A.; Mastragostino, M.; Arbizzani, C.; Pratt, D. A. *Chem.—Eur. J.* **2003**, *9*, 4997.
(51) Snelgrove, D. W.; Lusztyk, J.; Banks, J. T.; Mulder, P.; Ingold, K. U. *J. Am. Chem. Soc.* **2001**, *123*, 469.
(52) Litwinienko, G.; Ingold, K. U. *Acc. Chem. Res.* **2007**, *40*, 222.
(53) Kim, H.-Y.; Pratt, D. A.; Seal, J. R.; Wijtmans, M.; Porter, N. A. *J. Med. Chem.* **2005**, *48*, 6787.
(54) Nam, T.-G.; Rector, C. L.; Kim, H.-Y.; Sonnen, A. F. P.; Meyer, R.; Nau, W. M.; Atkinson, J.; Rintoul, J.; Pratt, D. A.; Porter, N. A. *J. Am. Chem. Soc.* **2007**, *129*, 10211.
(55) Li, B.; Harjani, J. R.; Cormier, N. S.; Madarati, H.; Atkinson, J.; Cosa, G.; Pratt, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 1394.
(56) Bowry, V. W.; Ingold, K. U.; Stocker, R. *Biochem. J.* **1992**, *288*, 341.
(57) Bowry, V. W.; Stocker, R. *J. Am. Chem. Soc.* **1993**, *115*, 6029.
(58) Ingold, K. U.; Bowry, V. W.; Walling, C.; Stocker, R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 45.
(59) Bowry, V. W.; Ingold, K. U. *Acc. Chem. Res.* **1999**, *32*, 27.
(60) Subsequent efforts have identified pyridoxine (Vitamin B_6) as a convenient synthetic precursor for bicyclic aminopyridinols.[61−63]
(61) Serwa, R.; Nam, T.-G.; Valgimigli, L.; Culbertson, S.; Rector, C. L.; Jeong, B.-S.; Pratt, D. A.; Porter, N. A. *Chem.—Eur. J.* **2010**, *16*, 14106.
(62) Nam, T.-G.; Ku, J.-M.; Park, H.-G.; Porter, N. A.; Jeong, B.-S. *Org. Biomol. Chem.* **2011**, *9*, 1749.
(63) Nam, T.-G.; Ku, J.-M.; Rector, C. L.; Choi, H.; Porter, N. A.; Jeong, B.-S. *Org. Biomol. Chem.* **2011**, *9*, 8475.
(64) Oleynik, P.; Ishihara, Y.; Cosa, G. *J. Am. Chem. Soc.* **2007**, *129*, 1842.
(65) Krumova, K.; Friedland, S.; Cosa, G. *J. Am. Chem. Soc.* **2012**, *134*, 10102.
(66) It should be mentioned that Hecht and co-workers enthusiastically followed up this work, preparing dozens of related compounds and performing model studies on their propensity to curtail oxidative stress in vitro. Unfortunately, to the best of our knowledge, the affinities of these compounds for TTP and their resultant metabolic stability and/or bioavailability have yet to be examined.[67−73]
(67) Lu, J.; Cai, X.; Hecht, S. M. *Org. Lett.* **2010**, *12*, 5189.
(68) Lu, J.; Khdour, O. M.; Armstrong, J. S.; Hecht, S. M. *Bioorg. Med. Chem.* **2010**, *18*, 7628.
(69) Khdour, O. M.; Lu, J.; Hecht, S. M. *Pharm. Res.* **2011**, *28*, 2896.
(70) Arce, P. M.; Khdour, O. M.; Goldschmidt, R.; Armstrong, J. S.; Hecht, S. M. *ACS Med. Chem. Lett.* **2011**, *2*, 608.
(71) Goldschmidt, R.; Arce, P. M.; Khdour, O. M.; Collin, V. C.; Dey, S.; Jaruvangsanti, J.; Fash, D. M.; Hecht, S. M. *Bioorg. Med. Chem.* **2013**, *21*, 969.

(72) Arce, P. M.; Goldschmidt, R.; Khdour, O. M.; Madathil, M. M.; Jaruvangsanti, J.; Dey, S.; Fash, D. M.; Armstrong, J. S.; Hecht, S. M. *Bioorg. Med. Chem.* **2012**, *20*, 5188.
(73) Khdour, O. M.; Arce, P. M.; Roy, B.; Hecht, S. M. *ACS Med. Chem. Lett.* **2013**, *4*, 724.
(74) Simpler aminopyridinols analgous to **10** have recently demonstrated activity in cell assays,[75] but these compounds are unlikely to be bioavailable.
(75) Omata, Y.; Saito, Y.; Yoshida, Y.; Jeong, B.-S.; Serwa, R.; Nam, T.-G.; Porter, N. A.; Niki, E. *Free Radical Biol. Med.* **2010**, *48*, 1358.
(76) The aminopyridinols are neither protonated on nitrogen nor deprotonated at the alcohol at physiological pH, that is, the pyridinols have pK_a values of ca. 10 and the pyridinum ions have pK_a values of ca. 5.[77]
(77) Nam, T.-G.; Nara, S. J.; Zagol-Ikapitte, I.; Cooper, T.; Valgimigli, L.; Oates, J. A.; Porter, N. A.; Boutaud, O.; Pratt, D. A. *Org. Biomol. Chem.* **2009**, *7*, 5103.
(78) de Heer, M. I.; Mulder, P.; Korth, H.-G.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **2000**, *122*, 2355.
(79) Lucarini, M.; Mugnaini, V.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 928.
(80) Xi, F.; Barclay, L. R. C. *Can. J. Chem.* **1998**, *76*, 171.
(81) Valgimigli, L.; Amorati, R.; Fumo, M. G.; DiLabio, G. A.; Pedulli, G. F.; Ingold, K. U.; Pratt, D. A. *J. Org. Chem.* **2008**, *73*, 1830.
(82) Foti, M. C.; Johnson, E. R.; Vinqvist, M. R.; Wright, J. S.; Barclay, L. R. C.; Ingold, K. U. *J. Org. Chem.* **2002**, *67*, 5190.
(83) Foti, M. C.; Amorati, R.; Pedulli, G. F.; Daquino, C.; Pratt, D. A.; Ingold, K. U. *J. Org. Chem.* **2010**, *75*, 4434.
(84) Amorati, R.; Valgimigli, L. *Org. Biomol. Chem.* **2012**, *10*, 4147.
(85) Foti, M. C.; Daquino, C.; DiLabio, G. A.; Ingold, K. U. *Org. Lett.* **2011**, *13*, 4826.
(86) Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2003**, *68*, 3433.
(87) Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2004**, *69*, 5888.
(88) Lucarini, M.; Pedulli, G. F.; Cipollone, M. *J. Org. Chem.* **1994**, *59*, 5063.
(89) Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Cabiddu, S.; Fattuoni, C. *J. Org. Chem.* **1996**, *61*, 9259.
(90) Amorati, R.; Ferroni, F.; Lucarini, M.; Pedulli, G. F.; Valgimigli, L. *J. Org. Chem.* **2002**, *67*, 9295.
(91) Amorati, R.; Ferroni, F.; Pedulli, G. F.; Valgimigli, L. *J. Org. Chem.* **2003**, *68*, 9654.
(92) Valgimigli, L.; Bartolomei, D.; Amorati, R.; Haidasz, E.; Hanthorn, J. J.; Nara, S. J.; Brinkhorst, J.; Pratt, D. A. *Beilstein J. Org. Chem.* **2013**, *9*, 2781.
(93) Malmström, J.; Jonsson, M.; Cotgreave, I. A.; Hammarström, L.; Sjödin, M.; Engman, L. *J. Am. Chem. Soc.* **2001**, *123*, 3434.
(94) Shanks, D.; Amorati, R.; Fumo, M. G.; Pedulli, G. F.; Valgimigli, L.; Engman, L. *J. Org. Chem.* **2006**, *71*, 1033.
(95) Kumar, S.; Johansson, H.; Engman, L.; Valgimigli, L.; Amorati, R.; Fumo, M. G.; Pedulli, G. F. *J. Org. Chem.* **2007**, *72*, 2583.
(96) Kumar, S.; Engman, L.; Valgimigli, L.; Amorati, R.; Fumo, M. G.; Pedulli, G. F. *J. Org. Chem.* **2007**, *72*, 6046.
(97) Kumar, S.; Johansson, H.; Kanda, T.; Engman, L.; Müller, T.; Jonsson, M.; Pedulli, G. F.; Petrucci, S.; Valgimigli, L. *Org. Lett.* **2008**, *10*, 4895.
(98) Amorati, R.; Pedulli, G. F.; Valgimigli, L.; Johansson, H.; Engman, L. *Org. Lett.* **2010**, *12*, 2326.
(99) Kumar, S.; Johansson, H.; Kanda, T.; Engman, L.; Müller, T.; Bergenudd, H.; Jonsson, M.; Pedulli, G. F.; Amorati, R.; Valgimigli, L. *J. Org. Chem.* **2010**, *75*, 716.
(100) Johansson, H.; Shanks, D.; Engman, L.; Amorati, R.; Pedulli, G. F.; Valgimigli, L. *J. Org. Chem.* **2010**, *75*, 7535.
(101) Amorati, R.; Valgimigli, L.; Dinér, P.; Bakhtiari, K.; Saeedi, M.; Engman, L. *Chem.—Eur. J.* **2013**, *19*, 7510.
(102) Selenium is an essential element in the human diet but is also highly toxic.[8]
(103) The known high toxicity of lead did not prevent its use as an octane enhancer (antiknock agent) in gasoline until quite late in the 20th century.
(104) A niche market for organoselenium antioxidants was found in the greases used to lubricate the mechanical parts (e.g., fuel rod drivers) in nuclear reactors.
(105) Garberg, P.; Engman, L.; Tolmachev, V.; Lundqvist, H.; Gerdes, R. G.; Cotgreave, I. A. *Int. J. Biochem. Cell Biol.* **1999**, *31*, 291.
(106) Nogueira, C. W.; Zeni, G.; Rocha, J. *Chem. Rev.* **2004**, *104*, 6255.
(107) Barclay, L. R. C. *J. Biol. Chem.* **1988**, *263*, 16138.
(108) Zahalka, H. A.; Robillard, B.; Hughes, L.; Lusztyk, J.; Burton, G. W.; Janzen, E. G.; Kotake, Y.; Ingold, K. U. *J. Org. Chem.* **1988**, *53*, 3739.
(109) Doba, T.; Burton, G. W.; Ingold, K. U. *Biochim. Biophys. Acta* **1985**, *835*, 298.
(110) Kharasch, M. S.; Nudenberg, W.; Mantell, G. J. *J. Org. Chem.* **1951**, *16*, 524.
(111) Packer, J. E.; Slater, T. F.; Willson, R. L. *Nature* **1979**, *278*, 737.
(112) Engman, L.; Persson, J.; Merenyi, G.; Lind, J. *Organometallics* **1995**, *14*, 3641.
(113) Thomas, J. R.; Tolman, C. A. *J. Am. Chem. Soc.* **1962**, *84*, 2930.
(114) Adamic, K.; Dunn, M.; Ingold, K. U. *Can. J. Chem.* **1969**, *47*, 287.
(115) Diphenylaminyl radicals do not react with O_2 on the laser-flash photolysis time scale. The significantly more reactive 2,2,6,6-tetramethylpiperidinyl radicals react with O_2 with a rate constant $< 2 \times 10^6$ M^{-1} s^{-1}.[116] See: DiLabio, G. A.; Litwinienko, G.; Lin, S.; Pratt, D. A.; Ingold, K. U. *J. Phys. Chem. A* **2002**, *16*, 11719.
(116) Brede, O.; Beckert, D.; Windolph, C.; Göttinger, H. A. *J. Phys. Chem. A* **1998**, *102*, 1457.
(117) Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4983.
(118) Bolsman, T. A. B. M.; Blok, A. P.; Frijns, J. H. G. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 310.
(119) Jensen, R. K.; Korcek, S.; Zinbo, M.; Gerlock, J. L. *J. Org. Chem.* **1995**, *60*, 5396.
(120) Brownlie, I. T.; Ingold, K. U. *Can. J. Chem.* **1967**, *45*, 2427.
(121) Hanthorn, J. J.; Amorati, R.; Valgimigli, L.; Pratt, D. A. *J. Org. Chem.* **2012**, *77*, 6895.
(122) Hanthorn, J. J.; Valgimigli, L.; Pratt, D. A. *J. Org. Chem.* **2012**, *77*, 6908.
(123) Hanthorn, J. J.; Pratt, D. A. *J. Org. Chem.* **2012**, *77*, 276.
(124) Jha, M.; Pratt, D. A. *Chem. Commun.* **2008**, 1252.
(125) Pratt, D. A.; Tallman, K. A.; Porter, N. A. *Acc. Chem. Res.* **2011**, *44*, 458.
(126) Di-*sec*-alkylamines are not RTAs because they readily participate in radical chain oxidations, i.e., $ROO^{\bullet} + (R'_2CH)_2NH \rightarrow ROOH + (R'_2CH)NHC(^{\bullet})R'_2 \rightarrow (R'_2CH)NHC(OO^{\bullet})R'_2$.
(127) In a paraffin oil at 130 °C, *n* values from ∼400 to ∼600 have been reported for tetramethylpiperidines and their nitroxides.[118]
(128) Allen, N. S. *Chem. Soc. Rev.* **1986**, *15*, 373.
(129) Gryn'ova, G.; Ingold, K. U.; Coote, M. L. *J. Am. Chem. Soc.* **2012**, *134*, 12979.
(130) Gugumus, F. *Polym. Degrad. Stab.* **1993**, *40*, 167.
(131) Pospíšil, J. In *Polysoaps/Stabilizers/Nitrogen-15 NMR; Advances in Polymer Science*; Springer-Verlag: Berlin/Heidelberg, 1995; Vol. *124*, p 87.
(132) Hodgson, J. L.; Coote, M. L. *Macromolecules* **2010**, *43*, 4573.
(133) Klemchuk, P. P.; Gande, M. E.; Cordola, E. *Polym. Degrad. Stab.* **1990**, *27*, 65.
(134) Ananchenko, G. S.; Fischer, H. *J. Polym. Sci. A: Polym. Chem.* **2001**, *39*, 3604.
(135) Paine, M. R. L.; Barker, P. J.; Blanksby, S. J. *Analyst* **2011**, *136*, 904.
(136) Paine, M. R. L.; Gryn'ova, G.; Coote, M. L.; Barker, P. J.; Blanksby, S. J. *Polym. Degrad. Stab.* **2014**, *99*, 223.
(137) Wiles, D. M.; Jensen, J. P. T.; Carlsson, D. J. *Pure Appl. Chem.* **1983**, *55*, 1651.
(138) Gugumus, F. *Polym. Degrad. Stab.* **1991**, *34*, 205.
(139) Hodgson, J. L.; Roskop, L. B.; Gordon, M. S.; Lin, C. Y.; Coote, M. L. *J. Phys. Chem. A* **2010**, *114*, 10458.

(140) "When you have eliminated the impossible, whatever remains, however improbable, must be the truth." Holmes, S. (quoted by A. C. Doyle in "The Sign of Four").
(141) Unpublished work from the Pratt laboratory.
(142) Jensen, R. K.; Korcek, S.; Mahoney, L. R.; Zinbo, M. *J. Am. Chem. Soc.* **1979**, *101*, 7574.
(143) Jensen, R. K.; Korcek, S.; Mahoney, L. R.; Zinbo, M. *J. Am. Chem. Soc.* **1981**, *103*, 1742.
(144) Jalan, A.; Alecu, I. M.; Meana-Paneda, R.; Aguilera-Iparraguirre, J.; Yang, K. R.; Merchant, S. S.; Truhlar, D. G.; Green, W. H. *J. Am. Chem. Soc.* **2013**, *135*, 11100.
(145) Ma, Y.; Loyns, C.; Price, P.; Chechik, V. *Org. Biomol. Chem.* **2011**, *9*, 5573.
(146) Block, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1135.
(147) Block, E. *Garlic and Other Alliums: The Lore and the Science*; The Royal Society of Chemistry: Cambridge, UK, 2010.
(148) Okada, Y.; Tanaka, K.; Fujita, I.; Sato, E.; Okajima, H. *Redox Rep.* **2005**, *10*, 96.
(149) Okada, Y.; Tanaka, K.; Sato, E.; Okajima, H. *Org. Biomol. Chem.* **2006**, *4*, 4113.
(150) Okada, Y.; Tanaka, K.; Sato, E.; Okajima, H. *Org. Biomol. Chem.* **2008**, *6*, 1097.
(151) Amorati, R.; Pedulli, G. F. *Org. Biomol. Chem.* **2008**, *6*, 1103.
(152) Koelewijn, P.; Berger, H. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 1275.
(153) Mahoney, L. R.; Mendenhall, G. D.; Ingold, K. U. *J. Am. Chem. Soc.* **1973**, *95*, 8610.
(154) Lynett, P. T.; Butts, K.; Vaidya, V.; Garrett, G. E.; Pratt, D. A. *Org. Biomol. Chem.* **2011**, *9*, 3320.
(155) Amorati, R.; Lynett, P. T.; Valgimigli, L.; Pratt, D. A. *Chem.—Eur. J.* **2012**, *18*, 6370.
(156) Paulsen, C. E.; Carroll, K. S. *Chem. Rev.* **2013**, *113*, 4633.
(157) Nakamura, N. *J. Am. Chem. Soc.* **1983**, *105*, 7172.
(158) McGrath, A. J.; Garrett, G. E.; Valgimigli, L.; Pratt, D. A. *J. Am. Chem. Soc.* **2010**, *132*, 16759.
(159) Zheng, F.; Pratt, D. A. *Chem. Commun.* **2013**, *49*, 8181.
(160) Russell, G. A. *J. Am. Chem. Soc.* **1956**, *78*, 1047.
(161) Hendry, D. G.; Russell, G. A. *J. Am. Chem. Soc.* **1964**, *86*, 2371.
(162) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1968**, *46*, 2655.
(163) Burton, G. W.; Ingold, K. U. *Science* **1984**, *224*, 569.
(164) Nesvadba, P. U.S. Patent 5,814,692 1998.
(165) Scaiano, J. C.; Martin, A.; Yap, G. P. A.; Ingold, K. U. *Org. Lett.* **2000**, *2*, 899.
(166) Bejan, E. V.; Font-Sanchis, E.; Scaiano, J. C. *Org. Lett.* **2001**, *3*, 4059.
(167) Font-Sanchis, E.; Aliaga, C.; Focsaneanu, K. S.; Scaiano, J. C. *Chem. Commun.* **2002**, 1576.
(168) Font-Sanchis, E.; Aliaga, C.; Cornejo, R.; Scaiano, J. C. *Org. Lett.* **2003**, *5*, 1515.
(169) Font-Sanchis, E.; Aliaga, C.; Bejan, E. V.; Cornejo, R.; Scaiano, J. C. *J. Org. Chem.* **2003**, *68*, 3199.
(170) Frenette, M.; Aliaga, C.; Font-Sanchis, E.; Scaiano, J. C. *Org. Lett.* **2004**, *6*, 2579.
(171) Aliaga, C.; Stuart, D. R.; Aspée, A.; Scaiano, J. C. *Org. Lett.* **2005**, *7*, 3665.
(172) Focsaneanu, K.-S.; Aliaga, C.; Scaiano, J. C. *Org. Lett.* **2005**, *7*, 4979.
(173) Focsaneanu, K.-S.; Scaiano, J. C. *Helv. Chim. Acta* **2006**, *89*, 2473.
(174) Frenette, M.; MacLean, P. D.; Barclay, L. R. C.; Scaiano, J. C. *J. Am. Chem. Soc.* **2006**, *128*, 16432.
(175) Filippenko, V.; Frenette, M.; Scaiano, J. C. *Org. Lett.* **2009**, *11*, 3634.
(176) Scaiano, J. C.; Tanner, M.; Weir, D. *J. Am. Chem. Soc.* **1985**, *107*, 4396.
(177) Benzylic radical stabilization, favorable stereoelectronics, delocalization of the unpaired electron onto the heteroatom, electron-withdrawing effects, and steric effects.
(178) Pratt, D. A.; Porter, N. A. *Org. Lett.* **2003**, *5*, 387.
(179) Pratt, D. A.; Mills, J. H.; Porter, N. A. *J. Am. Chem. Soc.* **2003**, *125*, 5801.
(180) Hexane, octane, hexadecane, benzene, anisole, and acetonitrile, listed in order of increasing viscosity for the alkanes and HBA activities thereafter.
(181) Korth, H.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 5274.
(182) Voica, A.-F.; Mendoza, A.; Gutekunst, W. R.; Otero Fraga, J.; Baran, P. S. *Nature Chem.* **2012**, *4*, 629.