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Carbon Radicals of Low Reactivity against Oxygen: Radically Different Antioxidants

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Most organic materials in the presence of atmospheric oxygen suffer from oxidative degradation, which initially leads to the formation of (hydro)peroxides. Indeed, every chemistry student (hopefully) learns about the danger imposed by the accumulation of peroxides in various organic solvents, in particular aliphatic ethers, on contact with air. Such autoxidations—initiated photochemically or by traces of redox-active transition metals—proceed generally by chain reactions with peroxyl radicals as chain-carrying intermediates [Eqs. (1)–(3)].[1,2]

Initiation:

$$X^\bullet + RH \rightarrow R^\bullet + RH \qquad (1)$$

Chain Propagation:

$$R^\bullet + O_2 \rightarrow ROO^\bullet \qquad (2)$$

$$ROO^\bullet + RH \rightarrow ROOH + R^\bullet \qquad (3)$$

The inhibition of such peroxidations is of major economical importance; one may for example consider the tendency of nutritional fats to become rancid[3] or the need to stabilize fuels, lubricants,[4] or polymers.[5]

On evolution, nature developed a series of effective antioxidants to counterattack the permanent oxidative degradation ("oxidative stress") of living organisms.[6,7] Vitamin E, with its most effective component α-tocopherol, is the most important lipophilic antioxidant in vivo,[8,9] and serves primarily to slow lipid peroxidation. In combination with the water-soluble antioxidant vitamin C (ascorbic acid), a synergetic protection effect often is observed.[10] Phenolic compounds with high antioxidative activity are found in a variety of plants, for example, quercetin (in oak wood) or resveratrol (in wine grapes). Furthermore, high antioxidative properties are attributed to the ubiquinone/ubiquinol-10 (coenzyme Q_{10}) or the carotinoides (for example, vitamin A). As can be inferred from the references cited above, most of the natural and artificial antioxidants are hydrogen-atom donors, predominately (poly)phenols or enones. The strength of such natural or synthetic antioxidants is based on the transfer of a hydrogen atom, and thus a chain-breaking antioxidant AH inhibits the peroxidation by trapping of the chain-carrying peroxyl radicals [Eqs. (4) and (5)]:[11]

Chain Termination:

$$ROO^\bullet + AH \rightarrow ROOH + A^\bullet \qquad (4)$$

$$ROO^\bullet + A^\bullet \rightarrow \text{nonradical products} \qquad (5)$$

In an ideal case, every molecule of antioxidant would dispose of two peroxyl radicals.

For a compound to be an effective antioxidant, the following properties are required:

a) The rate constant for hydrogen-atom transfer [Eq. (4)] must be much higher than that for the reaction in Equation (3), that is, $k_4 \gg k_3$.

b) The antioxidant radical $A^\bullet$ should not react with molecular oxygen, because this will compete with the reaction in Equation (5) and continue the chain. [Eqs. (6) and (7)].

$$A^\bullet + O_2 \rightarrow AOO^\bullet \xrightarrow{+RH} AOOH + R^\bullet \qquad (6)$$

$$A^\bullet + O_2 \rightarrow A_{-H} + HOO^\bullet \xrightarrow{+RH} HOOH + R^\bullet \qquad (7)$$

c) The radical $A^\bullet$ should not react with the substrate RH, as this also will continue the oxidation chain [Eq. (8)].

$$A^\bullet + RH \rightarrow R^\bullet + AH \qquad (8)$$

d) The antioxidant AH should not react with molecular oxygen (H abstraction) [Eq. (9)].

$$AH + O_2 \rightarrow HOO^\bullet + A^\bullet \qquad (9)$$

e) The ionization potential (IP) of AH should be high enough to prevent a proton-coupled electron transfer [Eq. (10)].

$$AH + O_2 \rightarrow [AH^{\bullet +} + O_2^{\bullet -}] \qquad (10)$$

Since the competition of Equations (3) and (4) is critical for the termination of the oxidation chain, a rather low homolytic bond dissociation enthalpy (BDE) of A−H is an essential factor for the antioxidative efficiency. In fact, within series of structurally related compounds (for example, phenols), a good inverse correlation between the BDE and the antioxidative power is often found. However, it is clear from conditions (a)–(e) that a good radical scavenger (radical trap) is not necessarily a good antioxidant. It is a frequently encountered misconception that com-

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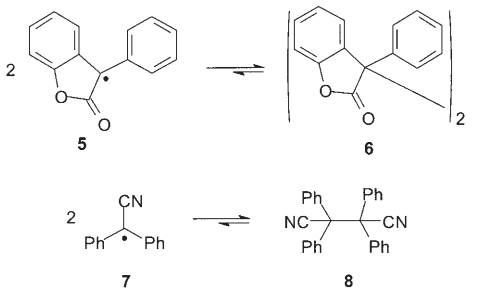
pounds that in principle may undergo facile H-atom transfer are considered good antioxidants, solely relying on the strength of the X–H bond (X = C, N, O, S) to be broken.[12]

Recently, Scaiano and co-workers introduced a new class of "radically different antioxidants".[13] These compounds, instead of being H-atom donors as the common antioxidants, thermally dissociate into carbon-centered radicals, thus taking advantage of the high rates of radical–radical reactions for the antioxidative activity.

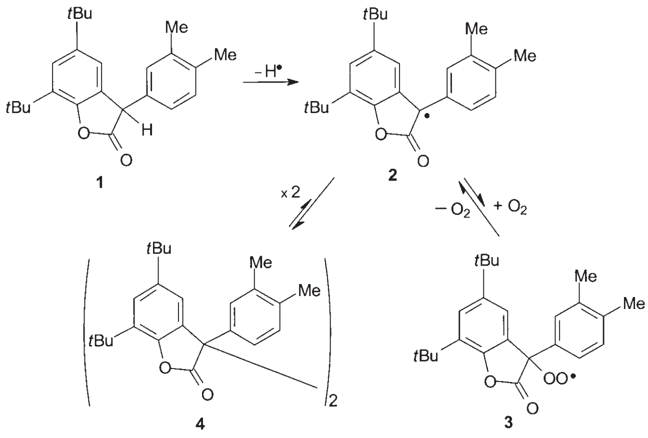
On investigation of the commercial lactone **1**, originally developed for the long-term protection of polymers,[14,15] it was observed that radical **2**, the initial hydrogen-abstraction product, did not react noticeably with molecular oxygen to give the expected peroxyl radical **3** (Scheme 1).[16] This observation was quite surprising as C-centered radicals generally react rapidly with oxygen.

Many resonance-stabilized C-radicals form dimers in high yield because other routes of decay are energetically unfavorable. If sufficiently sterically congested, such dimers have relatively weak C–C bonds, and thus may exist in thermal equilibrium with their radicals at ambient temperature. The classical example is the triphenylmethyl radical ($\mathrm{Ph_3C^{\bullet}}$), first described by Gomberg in 1900.[17] Such a situation was found by Scaiano and co-workers for the radical–dimer pairs **2**$\rightleftharpoons$**4**, **5**$\rightleftharpoons$**6**, and **7**$\rightleftharpoons$**8** (Scheme 2).[18,19] As a result of the lower steric hindrance in **2**, **5**, and **7** than in $\mathrm{Ph_3C^{\bullet}}$, their recombination gave only the "head-to-head" dimers **4**, **6**, and **8**.[20] The BDEs of the C–C bond in these dimers were determined to be in the range of 23–26 $\mathrm{kcal\,mol^{-1}}$,[19] and therefore it can be estimated that for **4**, for example, less than 0.1 % exist as free radicals at 30 °C for micromolar concentration.

The reaction of radicals **2**, **5**, and **7** with molecular oxygen was followed by laser-flash photolysis (LFP). In the μs time range after the photolytic generation of the radicals, no decay of their UV/Vis absorption could be monitored in oxygen-saturated benzene solution. In comparison, under similar conditions the diphenylmethyl radical ($\mathrm{Ph_2CH^{\bullet}}$) was effectively quenched within the same time range.[16] The inertness of **2**, **5**, and **7** to oxygen is quite remarkable in view of the fact that even the triphenylmethyl radical forms an isolable peroxide ($\mathrm{Ph_3COOCPh_3}$), as already reported by Gomberg.[17,21] Even if an equilibrium between **2** and **3** is taken into account, **2** is about 1000 times less reactive with oxygen than $\mathrm{Ph_3C^{\bullet}}$, which indicates that the low reactivity of **2**, **5**, and **7** with O_2 results from the electron-withdrawing effect of the C=O or C≡N group.[18]



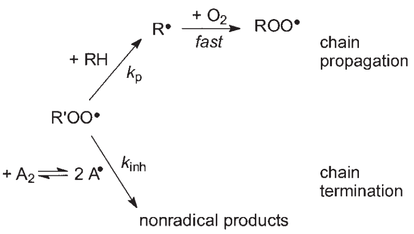
Scheme 2.



Scheme 1.

In marked contrast to their inertness to oxygen, radicals **2**, **5**, and **7** react rapidly with peroxyl radicals. Thus, despite the low equilibrium concentration of the related free radicals, dimers **4**, **6**, and **8** should be effective radical scavengers. This was confirmed by effective scavenging of carbon-centered radicals.[22]

The antioxidative activity of the radical-dimer systems was quantified by two standard assays: the inhibition of the autoxidation of cumene (isopropylbenzene) and styrene (vinylbenzene).[23] The reactions were initiated by thermal decomposition of 2,2′-azobisisobutyronitrile in chlorobenzene at 30 °C in the presence of air and the rapidly formed 2-cyanoisopropylperoxyl radical ($\mathrm{R'OO^{\bullet}}$) starts the reaction chain. According to Scheme 3, in the presence of dimers A_2 and radicals $A^{\bullet}$, a competition between chain propagation (oxygen consumption) and chain termination is established.



Scheme 3.

The antioxidative capacity therefore is determined by the ratio of the rate constant k_p of chain propagation and the rate constant k_{inh} of chain termination. To determine the activity of the antioxidants **4**, **6**, and **8**, the time dependence of oxygen consumption was monitored. Practically no oxygen consumption could be measured until the consumption of the dimers was complete and two peroxyl radicals were trapped in each reaction cycle. In fact the dimers turned out to be more effective than the widely used 3,5-di-*tert*-butyl-4-hydroxyanisole (DBHA), with **8** being the most potent compound. The inhibition rate constants k_{inh} of (2–7) $\times 10^5\,\text{M}^{-1}\,\text{s}^{-1}$ (compared with DBHA: $1.1\times10^5\,\text{M}^{-1}\,\text{s}^{-1}$ [24]) are lower than that of α-tocopherol ($3.2\times10^6\,\text{M}^{-1}\,\text{s}^{-1}$ [24]). However, taking into account the low stationary concentration of the corresponding free radicals, it can be estimated that the rate constants for reaction of **2**, **5**, and **7** with peroxyl radicals are in the range of $10^8\,\text{M}^{-1}\,\text{s}^{-1}$. Hence, with regard to the key trapping reaction, these radicals are in fact better antioxidants than vitamin E.

The dimer–radical couples presented here appear to be a promising new class of antioxidants. As a result of their hydrophobic nature, the systems investigated so far are only applicable in nonaqueous media. It will be interesting to see the results of more advanced applications, especially on models of lipid peroxidation. The antioxidative properties of common antioxidants that depend on the transfer of hydrogen atoms (for example, phenols), is strongly reduced in hydrogen-bond-forming solvents.[25] This restriction does not apply to the C-centered radicals described above.

A drawback to the practical application of the "radically different antioxidants" might be the long-term stability of the radical–dimer systems. Although a reaction with oxygen was not detected in the 100 μs time window after photolytic generation of the radicals, a very slow formation of peroxides (possibly of low solubility) might finally lead to deactivation of the antioxidants. This aspect needs to be investigated.

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