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Lactone-Derived Carbon-Centered Radicals: Formation and Reactivity with Oxygen

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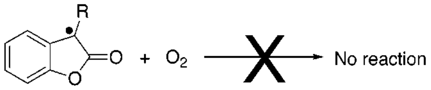
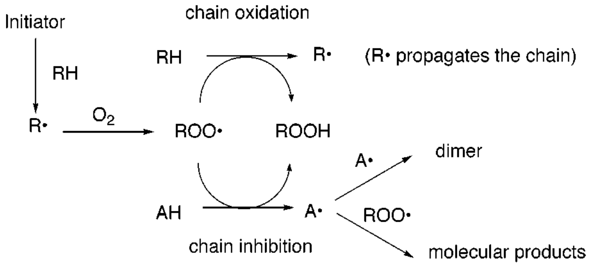
ABSTRACT



Several lactones were examined to test the reactivity of carbon-centered radicals toward oxygen. Notably, the radical derived from 2-coumaranone (4) is unreactive toward oxygen, while 2-cuomaranone itself shows enhanced reactivity toward hydrogen abstraction by alkoxyl radicals. We propose that five parameters influence diminished reactivity toward oxygen, i.e., (a) benzylic resonance stabilization, (b) unpaired spin delocalization on oxygen, (c) favorable stereoelectronic effects, (d) electron-withdrawing effects, and (e) steric effects.

Most autoxidations proceed by free-radical chain processes that involve peroxyl radicals.[1] An antioxidant can usually inhibit or retard the reaction with atmospheric oxygen and thus prevent the oxidative degradation of the material. Chain-breaking antioxidants have two key characteristics: first they are able to react readily with the free radicals involved in autoxidations, usually by hydrogen transfer processes, such as in the case of the peroxyl radicals involved in lipid peroxidation. Second, the radicals produced in the step mentioned above must terminate the autoxidation chain; this is usually achieved by forming a radical that does not react with oxygen. Thus, an antioxidant has to be a good hydrogen donor and also the radical produced must be unable to propagate the autooxidation chain (see Scheme 1).

Scheme 1 Autoxidation Mechanism



Phenols represent a structure found in many antioxidants, reflecting their excellent hydrogen donating ability and the fact that the phenoxyl radicals, just like many oxygen centered radicals, are unreactive toward oxygen.[2−4] Typical examples are vitamin E (α-tocopherol) and 2,6-*tert*-butyl-4-methylphenol, commonly referred as BHT (for butylated hydroxy toluene). An added bonus of phenols as antioxidants is their ability to produce radicals that not only do not propagate the autoxidation chain but also can trap a second radical, thus leading to a 2-to-1 stoichiometry for the radical-mediated antioxidation steps.[5,6]

Most carbon-centered radicals are highly reactive toward oxygen,[7] and as a result hydrogen-atom donors bearing reactive C−H bonds usually are not antioxidants; thus, molecules such as 1,4-cyclohexadiene are not antioxidants despite being good hydrogen donors.

Surprisingly, HP 136, an aryl-substituted lactone, is sold as an antioxidant for high-temperature polymer processing.

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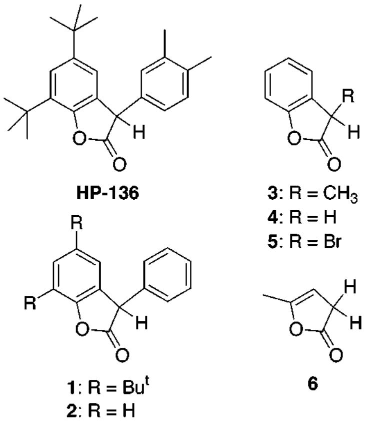
Scheme 2. Lactones Examined



Remarkably, the radical derived from HP-136 (Scheme 2) is essentially unreactive toward oxygen.[8] From a spectroscopic point of view, the HP-136 radical is virtually identical to the diphenylmethyl radical, which reacts with oxygen with a rate constant of $6.3 \times 10^8\ M^{-1}\ s^{-1}$ in cyclohexane at room temperature.[9]

This work was undertaken in an attempt to understand the structural parameters that make some lactone-derived carbon-centered radicals unreactive toward oxygen. To this effect we have examined the lactones in Scheme 2.

As part of this work, we have also examined the reactivity of various substrates toward alkoxyl radicals. This provides a comparison of their hydrogen donor ability on the basis of absolute rate constants using established laser flash photolysis methods.

The reactivity of the substrates toward alkoxyl radicals was determined by studying their reaction with *tert*-butoxyl radicals using laser flash photolysis techniques.[10] The radicals produced in these reactions have convenient absorptions that can be used to monitor their formation directly, a somewhat easier approach than the probe technique that can be used in the study of these reactions.[10] The *tert*-butoxyl radicals were produced by laser excitation (308 or 355 nm) of the peroxide in benzene (reaction 1 in Scheme 3). The growth of the radical signal reflects reaction 2 (k_2) and other forms of decay of *tert*-butoxyl (k_0), such as reaction with the solvent and β-cleavage. The experimental rate constant for the growth is given by eq 3 in Scheme 3.

Scheme 3. H-Abstraction by *tert*-Butoxyl Radicals

$$\mathrm{Bu^tOOBu^t} \xrightarrow{h\nu} 2\ \mathrm{Bu^tO\bullet} \qquad (1)$$

$$\mathrm{Bu^tO\bullet} + \mathrm{R\text{-}H} \longrightarrow \mathrm{Bu^tOH} + \mathrm{R\bullet} \qquad (2)$$

$$k_{\mathrm{exptl}} = k_0 + k_2\,[\mathrm{R\text{-}H}] \qquad (3)$$

The rate constants determined for representative substrates by using the approach of eq 3 are given in Table 1. Of particular interest is the unusually high reactivity of the 2-coumaranone series on comparison with other benzylic C−H bonds.

Table 1. Rate Constants for the Reactions of *tert*-Butoxyl Radicals with Hydrogen Donors and Radical Reactivity toward Oxygen

substrate	rate constant ($10^6\ M^{-1}\ s^{-1}$)	radical reacts with oxygen?[a]
toluene[10]	0.23	yes
diphenylmethane[13]	0.91	yes
HP-136	12.4	no
1	15.2	no
2	18.4	no
3	84	no
4	51	no
6	5.0	yes

[a] Based of laser flash photolysis work in a 100 μs time scale.

It seemed reasonable to assume that the ring substituents in HP-136 could not play any major role in the lack of reactivity of the radical toward oxygen. In fact, if one assumes that part of the role of the lactone moiety relates to its electron-withdrawing characteristics, then alkyl substituents could only neutralize in part this effect. In any event, **2** contains the basic framework of HP-136, but with no ring substituents. The same lack of reactivity of the radical toward oxygen was observed for **2**, as already reported for HP-136. The signal amplitudes were the same under oxygen or nitrogen, and the spectrum was virtually identical to that reported for the HP-136 radical. In fact, the absorption spectrum of the radical from **2** was already available in the literature.[11,12]

The photolysis of di-*tert*-butyl peroxide in the presence of 2-coumaranone **4** shows the formation of the radical shown in Figure 1. The visible band (350−450 nm) is far more intense than in the case of $PhCH_2^\bullet$ (420−470 nm);[14] the enhancement due to the presence of heteroatoms is well documented for a range of related radicals.[15] For example, the ketyl radical from acetophenone and related Norrish type II biradicals have absorption bands in the 420 nm region, with extinction coefficients approaching 1000 $M^{-1}\ cm^{-1}$.[16]

In an oxygen-saturated solution, the rate of decay of the 2-coumaranone radical (**7**) was essentially the same as under

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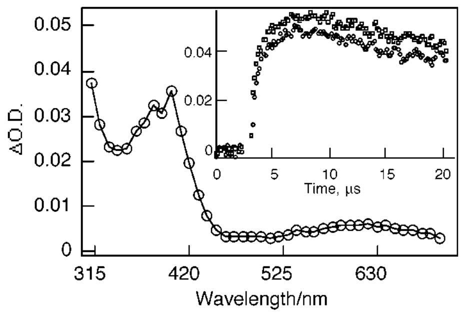
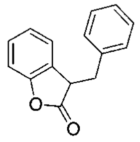


Figure 1. Transient absorption spectra recorded following 308 nm laser excitation of a sample containing 0.007 M 2-coumaranone **4** in benzene/di-*tert*-butyl peroxide (95/5) under nitrogen, 7.76 μs after the laser pulse. Inset: transient kinetic traces recorded at 400 nm under nitrogen (○) and oxygen (☐).

nitrogen. Monitoring at 400 nm, a comparison of nitrogen- and oxygen-saturated samples of 2-coumaranone (**4**) (see inset in Figure 1) shows that both the growth and the decay are not affected by oxygen, indicating that **7** is not reactive toward oxygen. A similar spectrum and a lack of reactivity toward oxygen were observed for the radical generated from 3-methyl-2-coumaranone (**3**). We were surprised by this observation, which suggests that even the second aromatic ring in HP-136 is not needed to restrict oxygen reactivity. To confirm the nature of this transient, 2-coumaranone radical was generated from the 3-bromo-2-coumaranone (**5**). Laser flash photolysis of **5** in cyclohexane shows the formation of a radical with a spectrum similar to the one obtained for 2-coumaranone **4**. Studying the kinetics in nitrogen- and oxygen-saturated samples, we observe that the rate of decay of the 2-coumaranone radical was essentially the same in both solutions, showing that this radical is not reactive toward oxygen. Part of the motivation to study **5** is related to the characterization of reaction products, vide infra.

Angelicalactone (**6**) reacts with *tert*-butoxyl faster than diphenylmethane, highlighting the importance of the lactone ring. However, the resulting radical (with weak maxima at 340 and 420 nm) reacts readily with oxygen.

Product studies were carried out on the bromo derivative **5**, where the question addressed relates to the resonance structures of the radical **7**, as shown above.



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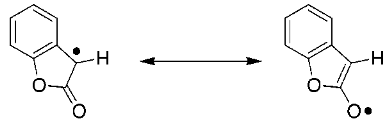
The solvent of choice for this work was toluene. Under these conditions, the bromine atoms formed upon photolysis abstract hydrogen from the solvent to produce benzyl radicals, which undergo radical−radical reactions. Lamp irradiation (Luzchem prototype photoreactor, UVB lamps, 3 h) of a deaerated 0.02 M toluene solution of 3-bromo-2-coumaranone led to complete consumption of the starting material. Analysis of the photolyzate by ^{1}H NMR and GC/MS revealed the formation of 3-benzyl-2-coumaranone **8**, dimers of 2-coumaranone, 2-coumaranone, and benzyl bromide. The structural assignment of the photoproduct **8** was confirmed by independent synthesis. The key process is the cross combination between radical **7** and benzyl, since this product should show the preferred site of reaction for **7**, demonstrating that the preferred reactivity of **7** is as a carbon-centered radical.



7a **7b**

The structure of the 2-coumaranone radical **7** was optimized via a density functional approach with the Spartan software package (version 5.0.3, Wavefunction, Inc., Irvine). A split-valence basis with a a single set of polarization functions added to each atom (DN**) was employed, and the chosen exchange and correlation functional was a gradient-corrected functional combining Becke's 1988 exchange functional and Perdew's 1986 correlation functional (BP86). The isocontour plots and spin densities were generated at the same level of theory. Figure 2 shows the corresponding spin density map.

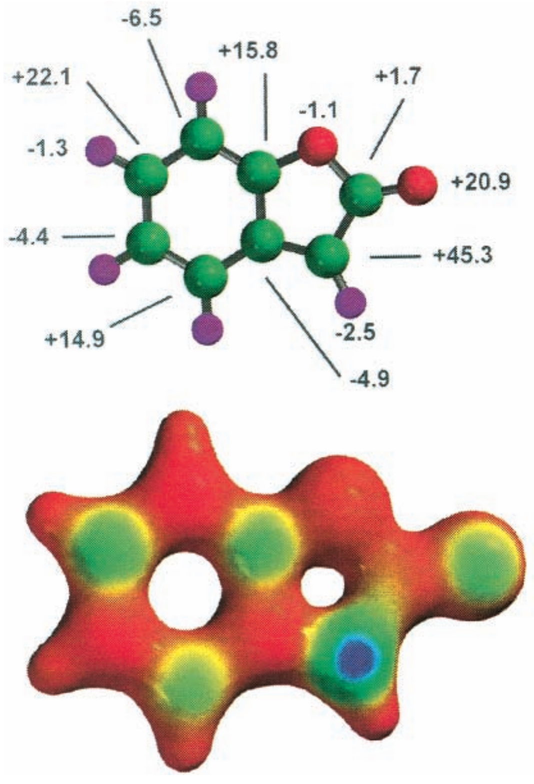
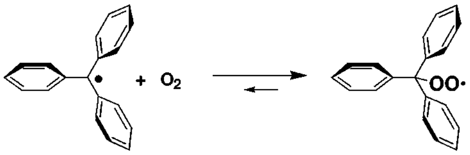


Figure 2. Unpaired spin distribution for the radical derived from **4**. Only values exceeding ±1% have been included.

The resonance delocalization of the unpaired electron on the carbonyl oxygen atom in this type of radicals could be provided by ESR data. It is known that 3,3′-diphenyl-3,3′-dibenzofuran-2,2′-dione[17] dissociates readily on heating in an inert solvent to form **2** radical. The ESR spectrum for **2** radical [$a^{H}_{ortho}(2H) = 2.51$ G, $a^{H}_{meta}(2H) = 0.97$ G, $a^{H}_{para}(1H) = 2.74$ G] suggests less interaction between the unpaired electron and the protons of the phenyl group than that reported for the diphenylmethyl radical[18] [$a^{H}_{ortho}(4H) = 3.05$ G, $a^{H}_{meta}(4H) = 1.22$ G, $a^{H}_{para}(2H) = 3.05$ G]. This is probably indicative of resonance delocalization of the unpaired spin on the aromaric ring in **2** radical.

From a different perspective, carbon-centered radicals are known to have greatly reduced reactivity toward oxygen in cases of extensive resonance stabilization, such as triphenylmethyl and 9-phenylfluorenyl. In the former example, this reduced reactivity results in reversible reaction with oxygen; the corresponding equilibrium has been examined by Howard and Ingold.[19] Under 1 atm of oxygen this equilibrium is largely displaced toward the peroxyl radical form, reaction 4. Note that in triphenylmethyl steric effects force all rings into a propeller-type conformation, where the rings are not in the preferred orientation for electron delocalization.



(4)

It is important to note that resonance stabilization and the possibility of delocalization on oxygen are not sufficient to prevent reactive behavior toward oxygen. Thus, the radical derived from methyl diphenylacetate (**9**) reacts readily with oxygen, despite the potential for oxygen-centered character.

It is believed that steric factors are most important in determining the reactivity of carbon-centered radicals. For example, the exceptional stability of the perchlorinated triarylmethyl radical has been attributed to steric factors.[20] However, the lack of reactivity of **7** toward oxygen suggests that the planarity of the molecule and the electronic effects due to the presence of the lactone ring are at least as important as bulky substituents in determining the lack of reactivity of lactone-derived radicals toward oxygen. We propose that the following factors control the reactivity of carbon-centered radicals with molecular oxygen: (a) benzylic resonance stabilization; (b) unpaired spin delocalization on oxygen, i.e., some oxygen-centered radical character; (c) favorable stereoelectronic effects, e.g., the forced planarity introduced by the presence of five-member rings, such as in the lactones; (d) electron-withdrawing effects contribute to some degree to diminishing reactivity toward oxygen; (e) steric effects preventing oxygen attack at the radical center.

There is no "golden rule" to decide which combination, or how many of these effects, are required, since the actual magnitude of each contribution is in itself important. Thus, much to our surprise, 2-coumaranone (**4**) gives a radical that is unreactive toward oxygen. With hindsight, radical **7** meets criteria (a−d) above, and only steric effects (e) are missing. Interestingly, it may be possible to design molecules that meet criterion (b) by shifting spin density toward other centers, such as nitrogen or sulfur.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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