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Radically Different Antioxidants: Thermally Generated Carbon-Centered Radicals as Chain-Breaking Antioxidants

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Oxidative processes involving molecular oxygen play a key role in the degradation of many materials. Autoxidation involves a radical chain reaction where each radical initiation can damage numerous molecules in a system.[1] Nature minimizes autoxidation by using chain-breaking antioxidants. Further, significant commercial efforts are invested in chain-breaking antioxidants to prevent degradation of organic materials.

Most small molecule chain-breaking antioxidants are hydrogen atom donors capable of trapping harmful chain-propagating peroxyl radicals. Vitamin E, a phenol, is an important chain-breaking antioxidant in lipids as it can donate hydrogen atoms to peroxyl radicals very efficiently.[2] After the initial hydrogen atom transfer, the radical of vitamin E or of any good chain-breaking antioxidant, must be sufficiently inert to the system and to oxygen as to not propagate the oxidative chain. Ideally, the resulting antioxidant radical will trap a second peroxyl radical.

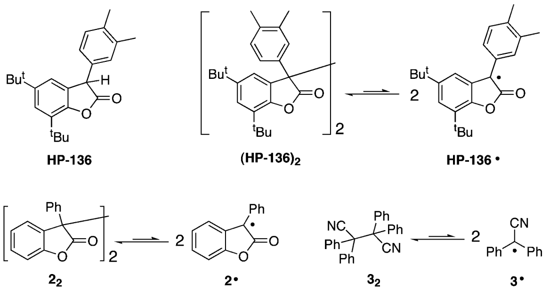
CIBA's Irganox HP-136 **(**HP-136**)** is a commercial chain-breaking antioxidant whose activity also relies on its hydrogen atom donating ability.[3] The resulting HP-136• radical is a carbon-centered radical. While most carbon-centered radicals react with oxygen to create more peroxyl radicals,[4] HP-136• and several other radicals, do not.[5] Interestingly the minor enol tautomer of HP-136 accounts for most of its hydrogen atom transfers.[6]

Many of these carbon-centered radicals form dimers held by weak C−C bonds (Scheme 1). The diamagnetic dimers are in thermal equilibrium with their nascent free radicals (Scheme 1). We measured bond dissociation energies between 23 and 26 kcal/mol for these well-behaved radical-dimer systems.[7a]

Our group has recently demonstrated the ability of some dimers, or more appropriately the radicals formed after thermal dissociation, to trap carbon-centered radicals.[7b] We now report that these dimers can prevent autoxidation in model systems by trapping peroxyl radicals very efficiently, even at temperatures as low as 30 °C.

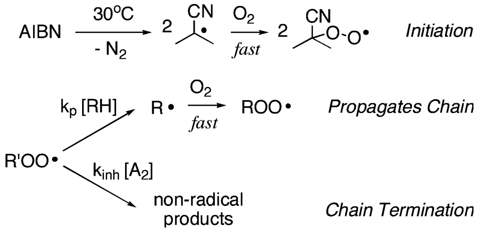
The ability of dimers to prevent autoxidation of cumene and styrene in chlorobenzene was measured by well-established competitive kinetic methods.[8] Briefly, the reactions were initiated by the thermal decomposition of AIBN under air to form peroxyl radicals. Subsequently, the peroxyl radical reacts with a substrate with a known rate constant, k_p,[9] to give a carbon-centered radical. The latter reacts rapidly with oxygen that yields another peroxyl radical, and so the chain reaction continues. The rate of the autoxidation is measured by monitoring oxygen uptake; note that every propagation cycle consumes one oxygen molecule. This reaction may be inhibited by addition of a small amount of chain-breaking antioxidants that efficiently traps peroxyl radicals. Scheme 2 summarizes the main chemical reactions that occur in our system with inhibition by dimers.

Scheme 1



HP-136 **(HP-136)$_2$** **HP-136•** **2_2** **2•** **3_2** **3•**

Scheme 2. Autoxidation of Cumene (RH) or Styrene under Air Initiated by 2,2′-Azo-bis(isobutyronitrile) (AIBN) and Inhibited by Dimers, **A$_2$**[a]



[a] Note the kinetic competition between propagation (oxygen uptake) and termination for the peroxyl radicals. A more detailed reaction scheme is included in the Supporting Information.

The activity of the antioxidant is represented by the rate constant of the bimolecular trapping reaction, k_{inh}, and the stoichiometric factor, n, defined as the number of peroxyl radicals trapped per antioxidant molecule.

Proper kinetic treatment gives the integrated form of the rate expression during the inhibited period,

$$\Delta[O_2]_t = -(k_p/\,k_{inh})[RH]\ln(1 - t/\tau) \qquad (1)$$

where t is time, τ is the inhibition period (defined as the time necessary to consume the antioxidant), and [RH] is the concentration of substrate, cumene or styrene. As long as there is significant oxygen uptake and enough propagation cycles (>4), one can estimate the k_{inh} by plotting $\Delta[O_2]$ vs $\ln(1 - t/\tau)$.

Figure 1 shows trials in cumene at 30 °C. All dimers completely inhibited the autoxidation (no significant oxygen uptake) with $n = 2$. In this system, they behave as ideal antioxidants. Surprisingly, HP-136 showed no measurable activity in this system at similar concentrations. We did observe a slight inhibition when HP-136 was added in much greater concentration (see Figure 1, trace F), and it was possible to estimate its activity as $<1.0 \times 10^2$ M^{-1}•s^{-1} (see Supporting Information for kinetic treatment). This may explain why HP-136 is more widely used as an antioxidant for high-temperature processing and long-term protection.[3] In fact, radical

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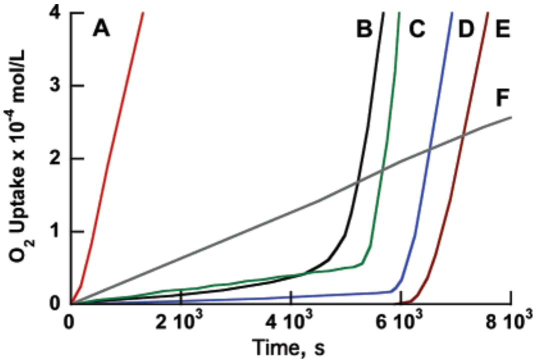

Figure 1. Profiles of oxygen-uptake during AIBN (~17 mM) initiated autoxidation of cumene (~5.4 M) in chlorobenzene at 30 °C under air. Curve A: Uninhibited oxygen-uptake. Curve B: inhibited by 3,5-di-*tert*-butyl-4-hydroxyanisole (DBHA), 4.3 μM. Curve C: Inhibited by $\mathbf{2}_2$, 5.34 μM. Curve D: Inhibited by $(HP\text{-}136)_2$, 5.7 μM. Curve E: Inhibited by $\mathbf{3}_2$, 5.7 μM. Curve F: Inhibited by HP-136, 0.24 mM.

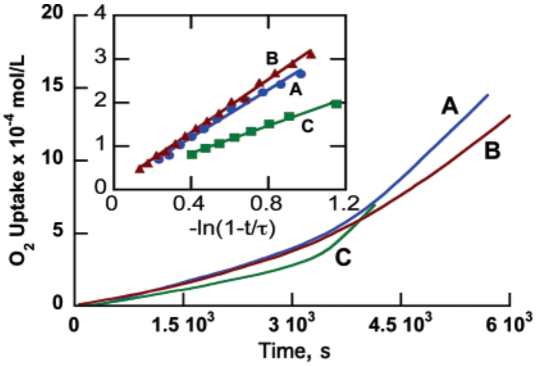

Figure 2. Profiles of oxygen-uptake during AIBN, ~17 mM, initiated autoxidation of styrene, ~2.5 M, in chlorobenzene at 30 °C under air. Curve A: Inhibited by $(HP\text{-}136)_2$, 13.0 μM. Curve B: inhibited by $\mathbf{3}_2$, 6.6 μM. Curve C: Inhibited by $\mathbf{2}_2$, 14.8 μM. Inset: Plot of oxygen-uptake (same *y*-axis as figure) in function of $-\ln(1 - t/\tau)$ as described in eq 1 for each respective traces in the figure.

trapping by HP-136 can generate the dimers that are the subject of this contribution.

To obtain antioxidant activities for the dimers, we used a styrene system in which a significant oxygen uptake during the inhibition period was observed. At 30 °C, all dimers performed well in preventing the autoxidation of styrene, giving defined inhibition periods (Figure 2) from which we could obtain k_{inh} and n, shown in Table 1.

With antioxidant activities, k_{inh}, of $(2 - 7) \times 10^5$ M^{-1}•s^{-1}, the dimers compare favorably with hindered phenols such as 3,5-di-*tert*-butyl-4-hydroxyanisole (DBHA), $k_{\text{inh}} = 1.1 \times 10^5$ M^{-1}•s^{-1} but are still far from the 3.2×10^6 M^{-1}•s^{-1} inhibition rate constant reported for vitamin E.[10] Nonetheless, these molecules represent a new class of antioxidants that take advantage of the very fast nature of radical−radical reactions. From the thermodynamic data available for $(HP\text{-}136)_2$,[7a] we can calculate that, at 30 °C and 13 μM dimer concentration, only ~0.08% of the dimer is dissociated into radicals. From this, we can estimate a rate constant of $\sim 1 \times 10^8$ M^{-1}•s^{-1} for the trapping of peroxyl radicals by HP-136•. These radicals are, in fact, better antioxidants than vitamin E itself.

Increasing the temperature of a dimer-containing system increases the concentration of carbon-centered radicals and thus, should increase the antioxidant activity. From 30 °C to 45 °C, the antioxidant activity for $(HP\text{-}136)_2$ increases by a factor of 2.42 to 1.04×10^6 M^{-1}•s^{-1}, and the radical concentration is calculated to increase by a factor of 2.46.

Table 1. Kinetic Data for Trapping Peroxyl Radicals by Dimers.

inhibitor	substrate	T (°C)	BDE[a] (kcal/mol)	n[b]	k_{inh}, (10^4 M^{-1}•s^{-1})
vitamin E[c]	styrene	30	−	2	320
$(HP\text{−}136)_2$	cumene	30	23	1.9	*no O_2 uptake*
$(HP\text{−}136)_2$	styrene	30	23	~0.8	43 ± 9
$(HP\text{−}136)_2$	styrene	45	23	~0.4	104 ± 17
$\mathbf{2}_2$	cumene	30	24	2.1	*no O_2 uptake*
$\mathbf{2}_2$	styrene	30	24	~0.6	67 ± 6
$\mathbf{3}_2$	cumene	30	26	2.0	*no O_2 uptake*
$\mathbf{3}_2$	styrene	30	26	~1.4	22 ± 7
$\mathbf{3}_2$	styrene	45	26	~1.0	~61
DBHA[c]	styrene	30	−	2	11

[a] Bond dissociation energies from reference 7a. [b] $n = \tau\, R_i/[\mathbf{A_2}]_o$. Cumene gave more accurately measurable τ values (and therefore n values) than styrene because both k_p and k_t (self-termination rate constant) are significantly smaller in cumene than in styrene.[11] Possible mechanisms for the lower n values measured in styrene are mentioned in the Supporting Information. [c] k_{inh} for α-tocopherol and 3,5-di-*tert*-butyl-4-hydroxyanisole from reference 10.

The antioxidant activities of all common antioxidants that function by hydrogen transfer have their activities reduced in polar media by intermolecular hydrogen bonding;[12] however, these carbon-centered radicals should be less sensitive to this effect.

In conclusion, we discovered a new class of thermally activated chain-breaking antioxidants based on a radical−dimer equilibrium. An application for a patent has been filed by one of us.[13]

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Supporting Information Available: Expanded reaction list for Scheme 2, kinetic treatment for determining k_{inh} for HP-136 from Figure 1F, proposed mechanism for lower n values in styrene, and video of the thermal dissociation of dimers in toluene. This material is available free of charge via the Internet at http://pubs.acs.org.

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