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Solvent-Independent Antioxidant Activity from Thermally Generated Carbon-Centered Radical Antioxidants

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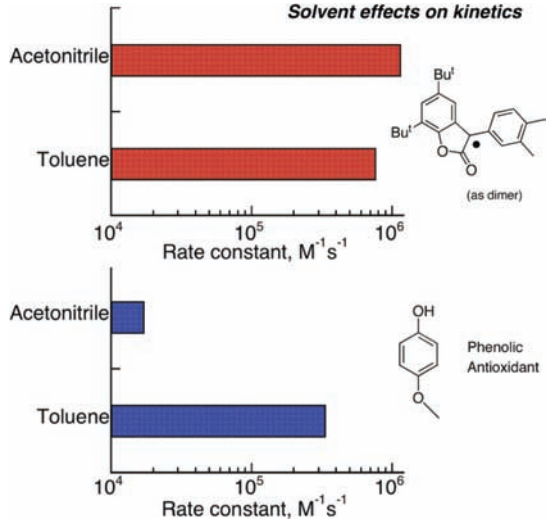
ABSTRACT



A new and unusual class of chain-breaking antioxidants has been discovered, where the actual antioxidant is, paradoxically, a carbon-centered radical. Properties of these molecules are currently being studied. The solvent dependence on antioxidant activity of the HP-136 dimer has been measured, in solvents of varying H-bond accepting ability, by the inhibited oxygen uptake (IOU) method. As anticipated, the HP-136 dimer was found to show much less solvent effect on antioxidant activity than a representative phenolic antioxidant.

Degradation of various materials, including biological systems, is often a result of oxidative damage caused by free radical reactions. The harmful nature of free radicals stems from the fact that a small number of radicals can initiate self-propagating chain reactions, thus amplifying damaging effects.[1,2] Under air, the propagation reaction is often an autoxidation, where peroxyl radicals are the key reactive species involved in oxidizing a substrate and sustaining the chain reaction cycle (Scheme 1).

Autoxidations can be retarded by the addition of antioxidants. Most small-molecule, chain-breaking antioxidants hinder the propagation cycle by reacting with peroxyl radicals to give products that do not participate in the propagation reaction, thus stopping further oxidative damage. This means that, for the inhibition of autoxidation, one of the key characteristics of an antioxidant is its lack of reactivity and the lack of reactivity of any intermediate radicals, toward molecular oxygen.[3] Common chain-breaking antioxidants that fit these criteria are

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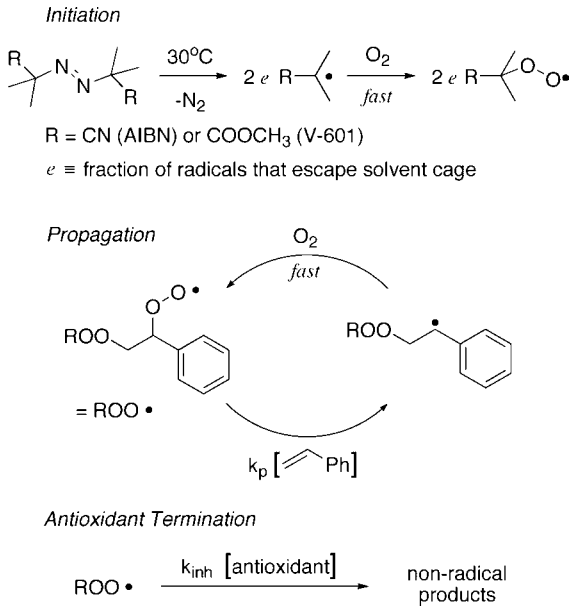
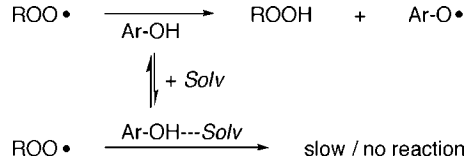
Scheme 1. Initiation, Autoxidation Chain Reaction of Styrene via Oxidative Polymerization, and Antioxidant Termination



phenolic molecules such as α-tocopherol (Vitamin E). They act by trapping peroxyl radicals via hydrogen atom transfer.[4,5] Ideally, a single antioxidant molecule can trap two peroxyl radicals[2] (stoichiometric factor, $n = 2$). Hydrogen donors that yield carbon-centered radicals are rarely good antioxidants since most carbon-centered free radicals react rapidly with oxygen to give a peroxyl radical,[6] thus propagating the oxidation chain.

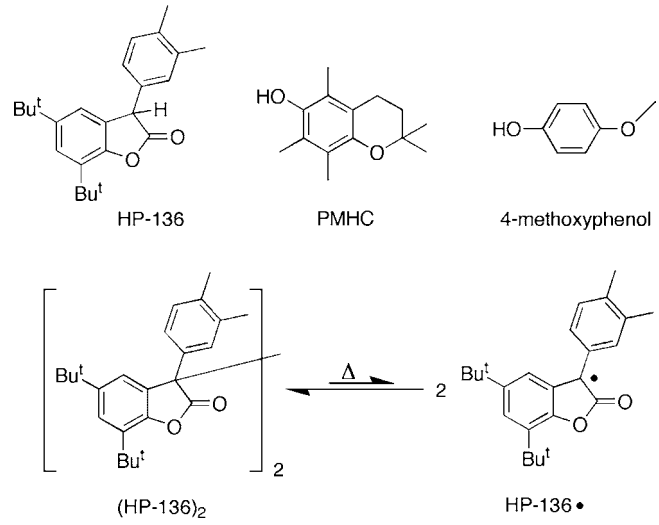
Due to the presence of an O−H bond, common phenolic antioxidants tend to be very sensitive to solvent effects. Hydrogen bonding with the solvent lowers the phenol's hydrogen-atom donating ability; as a result, their antioxidant activity in H-bond accepting (HBA) solvents dramatically decreases (Scheme 2).[5,7]

Scheme 2. Effect of H-Bond Accepting Solvent (*Solv*) on Common Phenolic Antioxidants (Ar−OH)



Recently, our group discovered a new and unusual class of antioxidants, where the actual antioxidant is, paradoxically, a carbon-centered free radical.[8,9] Whereas most carbon-centered radicals react rapidly with oxygen,[6] these molecules do not and instead prefer to react with each other to form head-to-head dimers held together by atypically weak carbon−carbon bonds.[9] In solution, these dimers are present in thermal equilibrium with their radicals (Scheme 3). These

Scheme 3. Structure of the Relevant Compounds



dimers have been referred to as having "dynamic stability" through constant dissociation to the carbon-centered radicals and reassociation of the latter. The bond dissociation energies of the dimers in these well-behaved equilibria have been found to lie between 23 and 26 kcal/mol.[9] In the present work, we examine solvent effects on the antioxidant activity of the HP-136 dimer (Scheme 3). This dimer was chosen because it was the best behaved from structurally related dimers previously tested.[8]

In contrast to common phenolic antioxidants that exhibit strongly solvent-dependent antioxidancy due to hydrogen bonding (Scheme 2), the HP-136 radical cannot hydrogen bond at its reactive site and is thus expected to exhibit little or no solvent effect on its antioxidant activity in HBA solvents.[10] This expectation was tested by measuring antioxidant activities of the HP-136 dimer, in a range of solvents, by the inhibited oxygen uptake (IOU) method. The results are compared with results for a representative phenolic antioxidant, 4-methoxyphenol (Scheme 3).

Solvents were chosen to cover a range of HBA activities as defined by Abraham et al.'s β_2^H scale[11] (range 0.00 for non-HBA solvents such as alkanes to 1.00 for HMPA, a strong H-bond acceptor).

The IOU is a very well-established technique for the measurement of antioxidant activities of molecules.[4,12,13]

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The oxygen uptake curves provide a means for estimating the antioxidant activities of molecules by measuring their relative inhibition rate constants, k_{inh}.[4,12,13]

Integrating the rate expression during the inhibition period yields eq 1[13]

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

where t is time; [RH] is the concentration of the substrate, styrene; k_p is the propagation rate constant (41 M^{-1} s^{-1} for styrene[14] at 30 °C); and τ is the inhibition period, estimated from the intercept of inhibited and uninhibited rates of oxygen uptake and defined as the time it takes to consume the antioxidant. Values of k_{inh} are obtained from the linear plot of $\Delta[O_2]$ vs $-\ln(1 - t/\tau)$, provided a substrate that has a known k_p, such as styrene, is used (Figure 2S, Supporting Information). However, the IOU method for measuring k_{inh} requires that there be a significant number of propagation cycles during the inhibition period (chain length >4), so that there is a measurable competition between the propagation and inhibition reactions.[4,13] PMHC (2,2,5,7,8-pentamethyl-6-hydroxychroman) is a Vitamin E analogue that is known to trap two peroxyl radicals (i.e., it has a stoichiometric factor, n, of 2). However, in the weaker HBA solvents PMHC is too strong an antioxidant to reliably measure k_{inh} (i.e., chain lengths are often <4). For this reason, a weaker antioxidant, 4-methoxyphenol, whose k_{inh} values could be measured more reliably, was employed for comparative purposes. PMHC was, however, employed to determine the rate of initiation of autoxidation, R_i, and later to calculate stoichiometric factors, n, using eq 2

$$R_i = n[\text{antioxidant}]/\tau \quad (2)$$

Table 1 and Figure 1 summarize the results obtained. As anticipated, the HP-136 dimer exhibited little or no solvent effect on its antioxidant activity compared with large solvent effects for 4-methoxyphenol. With increasing HBA activity of the solvent, the k_{inh} values for 4-methoxyphenol decrease markedly, whereas the k_{inh} values of the HP-136 dimer are almost invariant, indicating that the antioxidant activity of the HP-136 dimer is not reduced with variations in the HBA activity of the solvent.

Table 1. Solvent Effects on Kinetic Data for Inhibition of Styrene Autoxidation at 30 °C

	HP-136 dimer			4-methoxyphenol	
solvent	β_2^H	n	k_{inh} (10^4 M^{-1} s^{-1})	n	k_{inh}[a] (10^4 M^{-1} s^{-1})
chlorobenzene	0.09	0.89	61 ± 10	2.27	37 ± 10
toluene	0.14	1.20	75 ± 28	2.65	33 ± 2
anisole	0.26	1.47	45 ± 10	3.10	13.1 ± 0.8
ethanol	0.44	1.18	73 ± 21	n/a	(4.8)[b]
acetonitrile	0.44	0.94	113 ± 39	n/a	1.7 ± 0.3
n-butanol	0.45	0.89	124 ± 63	n/a	4.7 ± 2.6

[a] For solvents ethanol, acetonitrile, and *n*-butanol, no clear inhibition period was observed when using 4-methoxyphenol as an antioxidant. Higher antioxidant concentrations and a slightly different kinetic treatment were necessary to obtain k_{inh} (see Supporting Information). [b] This rate constant was found to vary from experiment to experiment and should only be regarded as a rough estimate. It has not been included in Figure 1.

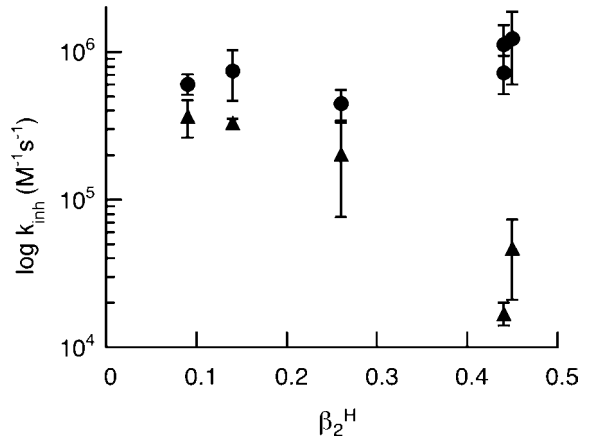

Figure 1. Solvent effects on antioxidant activities (k_{inh}) of HP-136 dimer (●) and 4-methoxyphenol (▲). Hydrogen-bond accepting abilities of solvents are described by their Abraham factors, β_2^H (chlorobenzene = 0.09, toluene = 0.14, anisole = 0.26, ethanol = 0.44, acetonitrile = 0.44, *n*-butanol = 0.45). Error bars ± 1 st. dev.

The difference in solvent effects on the antioxidant behavior of the HP-136 dimer and 4-methoxyphenol is clearly evident from the oxygen uptake curves in Figure 2.

In chlorobenzene ($\beta_2^H = 0.09$), both compounds give an inhibition period and thus have antioxidant activity. However, in acetonitrile ($\beta_2^H = 0.44$), 4-methoxyphenol shows no induction period though the rate of oxidation is lower than in the absence of any antioxidant; i.e., in acetonitrile this compound has become an autoxidation retarder, rather than an inhibitor. The HP-136 dimer, on the other hand, shows a well-defined inhibition period in acetonitrile that is, in fact, slightly better defined than it was in chlorobenzene. Note also that PMHC is not as strong an inhibitor in acetonitrile as it is in chlorobenzene, reflecting the fact that even such a very strong phenolic antioxidant is subject to HBA solvent effects.[7,15]

It should be noted that the antioxidant activity for dimers is expressed in terms of HP-136 dimer concentration; this allows k_{inh} to be compared with those obtained for common phenolic antioxidants. The active antioxidant is, of course, the carbon-centered radical form, not the dimeric species. This approach will yield k_{inh} values that show some dependence on the initial dimer concentration (see Supporting Information).

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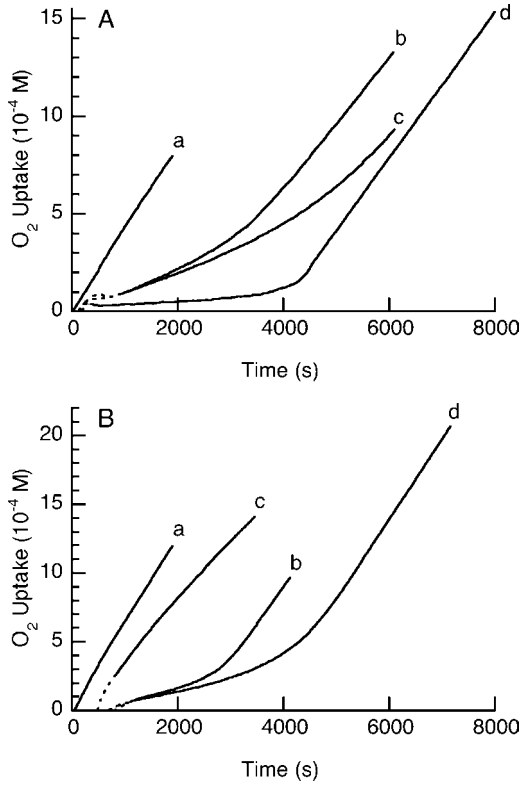

Figure 2. (A) Oxygen uptake curves for autoxidation of styrene, ~2.6 M, in chlorobenzene, initiated with azo-bis(isobutyronitrile), AIBN, ~18.1 mM, at 30 °C. Curve a: uninhibited oxygen uptake. Curve b: inhibited by the HP-136 dimer, ~9.1 μM. Curve c: inhibited by 4-methoxyphenol, ~4.6 μM. Curve d: inhibited by 2,2,5,7,8-pentamethyl-6-hydroxychroman (PMHC), ~4.6 μM. (B) Oxygen uptake curves for autoxidation of styrene, ~2.6 M, in acetonitrile, initiated with AIBN, ~18.3 mM, at 30 °C. Curve a: uninhibited oxygen uptake. Curve b: inhibited by the HP-136 dimer, ~7.7 μM. Curve c: inhibited by 4-methoxyphenol, ~13.2 μM. Curve d: inhibited by PMHC, ~4.6 μM. Dashed lines indicate equilibration period of the system.

The stoichiometric factor for the HP-136 dimer during styrene autoxidation is closer to 1.0 than to the 2.0 expected on the basis of two radicals from each dimer molecule, a result that has been previously discussed.[8] Values of n greater than two are observed for 4-methoxyphenol and are likely due to the formation of secondary antioxidants during oxidation of this compound. We have shown earlier that $n = 2$ for the HP-136 dimer when cumene is the autoxidizing substrate.[8] This is common when cumene is the substrate.[16]

In summary, one of our newly discovered "*radically different antioxidants*", the HP-136 dimer, has been shown to retain full antioxidant activity in HBA solvents. This may provide a significant advantage over common phenolic antioxidants in industrial applications involving polarity variations of the reaction environment. Another useful characteristic of such dimers is that they are thermally activated[9] which should make them even better antioxidants at the higher operating temperatures.

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Supporting Information Available: Experimental details, synthesis procedures, materials, and kinetic treatment. This material is available free of charge via the Internet at http://pubs.acs.org.

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