

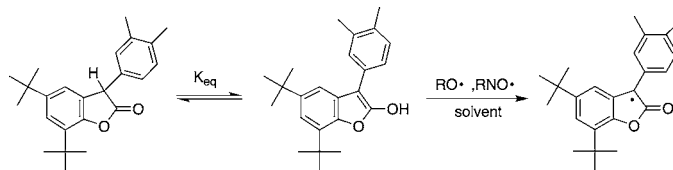
# Solvent Effects on Hydrogen Abstraction Reactions from Lactones with Antioxidant Properties

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## ABSTRACT

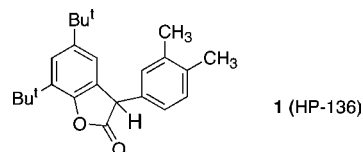


Solvent effects on the kinetics for hydrogen abstraction from a lactone antioxidant were determined for alkoxy and nitroxyl radicals; their reactivity differ by about 7 orders of magnitude. A decrease by  $\sim 12$  and  $\sim 35$  were determined for H-abstraction by *tert*-butoxyl and nitroxyl radicals, respectively, upon changing the solvent from hexane to acetonitrile. Results of solvent and isotope studies indicate that the antioxidant properties of lactone antioxidants should be attributed to the enol, not the lactone.

Chain-breaking antioxidants are normally efficient hydrogen donors that produce radicals that do not react with molecular oxygen. Radicals derived from phenolic antioxidants are frequently able to trap a second radical, thus terminating two autoxidation chains.<sup>1</sup> The rate constants for hydrogen abstraction from phenolic OH groups are strongly influenced by the solvent properties; the hydrogen donor ability of the substrate (or antioxidant) depends on the hydrogen bond acceptor properties of the solvent, since in the case of phenols hydrogen transfer involves predominantly the free donor, with little or no reactivity arising from the hydrogen bonded phenol.<sup>2,3</sup> The case of vitamin E, which exhibits a large kinetic solvent effect in its reaction with alkoxy radicals, as well as 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals, is well understood.<sup>4</sup>

In this work, we have examined solvent effects on the rate constant of hydrogen abstraction ( $k_H$ ) from **1**, an isobenzofuranone commercially available as HP-136; **1** is sold as an

antioxidant for polymeric processes, and is a moderately good hydrogen donor toward alkoxy radicals.<sup>5,6</sup> Hydrogen transfer leads to a carbon-centered radical that does not react with molecular oxygen, a desirable characteristic for an antioxidant; we conclude that the reactivity should be attributed to the enol form in equilibrium with the lactone.



The present study was carried out employing alkoxy and nitroxyl radicals, two radicals with very different reactivities in hydrogen atom abstraction reactions. Alkoxy radicals were generated by laser flash photolysis (LFP) of di-*tert*-butyl

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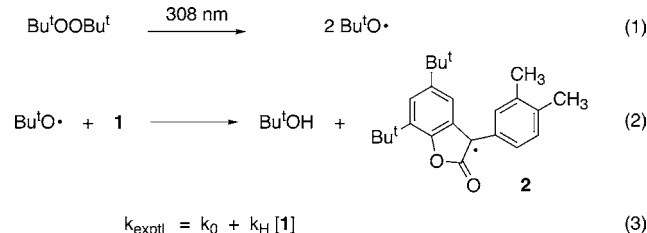
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peroxide (5%) in polar and nonpolar solvents using 308 nm laser pulses for excitation (see Scheme 1 and the Supporting

**Scheme 1.** Hydrogen Abstraction by *tert*-Butoxyl Radicals



Information). The *tert*-butoxyl radicals abstract hydrogen to produce the carbon centered radical and *tert*-butyl alcohol. The growth of the radical signal reflects H-abstraction ( $k_{\text{H}}$ ) and any other forms of decay of *tert*-butoxyl radicals such as  $\beta$ -cleavage and reaction with solvent ( $k_0$ ). The experimental rate constant for the growth is given by eq 3 and the methodology is the same one used earlier.<sup>5</sup> The rate constants determined from plots of  $k_{\text{exptl}}$  vs  $[\mathbf{1}]$  in different solvents are given in Table 1. The LFP technique reveal unequivocally

**Table 1.** Rate Constants for Hydrogen Abstraction from **1** or Its Enol by Alkoxy and Nitroxyl Radicals

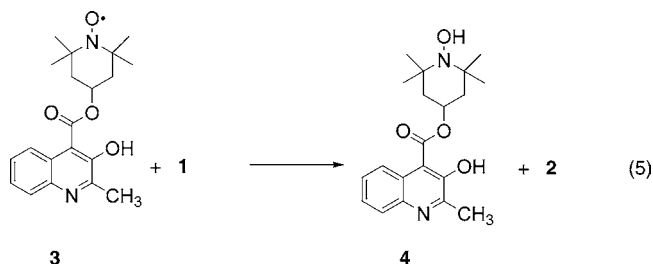
solvent	$k_{\text{H}}^{\text{RO}^\bullet}$ , $10^7 \text{ M}^{-1} \text{ s}^{-1}$	$k_{\text{H}}^{\text{NO}^\bullet}$ , $\text{M}^{-1} \text{ s}^{-1}$	$\beta_2^{\text{H}}$
<i>n</i> -hexane	9.4	5.7	0
<i>n</i> -heptane	7.7		
<i>n</i> -octane	5.2	4.8	0
hexadecane	4.8		
benzene	3.4	0.53	0.14
anisole	2.2	0.35	0.26
methanol		0.33	0.41
methanol- <i>d</i> <sub>4</sub>		0.033	0.41
methanol/AcH <sup>a</sup>		0.35	
methanol- <i>d</i> /AcD <sup>b</sup>		0.028	
acetonitrile	0.8	0.16	0.44

<sup>a</sup> Containing 1% (v/v) acetic acid. <sup>b</sup> Containing 1% (v/v) acetic acid-*O-d*.

the structure of the radical produced, but does not identify if the reactive molecule is HP-136 or its enol (vide infra); the arguments presented in this contribution clearly favor the latter.

Measurement of nitroxide radical reactivity requires the implementation of a different methodology involving the use of a *pre-fluorescent* TEMPO probe. Nitroxides have been suggested to have a reactivity that parallels that for peroxy radicals.<sup>7</sup> In this study, the probe used is quinoline-TEMPO (**3**, Scheme 2), a prefluorescent probe in which the fluorescence of the quinoline chromophore is quenched by the paramagnetic TEMPO moiety. Upon hydrogen transfer from **1** to the nitroxyl radical the diamagnetic hydroxylamine (**4**)

**Scheme 2.** Hydrogen Abstraction by Prefluorescent Nitroxyl Radical Probes



is formed, and in the process the fluorescence of the quinoline moiety is restored.<sup>8</sup> This allows the rate of hydrogen transfer ( $k_{\text{obs}}$ ) to be determined directly from growth of the fluorescence of the probe as a function of time, according to eqn 4, where  $I^\infty$ ,  $I^0$ , and  $I^t$  represent the fluorescence intensities in the plateau region, initially and at time “*t*”, respectively. Details of the method have been reported elsewhere.<sup>8</sup>

$$\ln\left(\frac{I^\infty - I^0}{I^\infty - I^t}\right) = k_{\text{obs}}t \quad (1)$$

The rate constants for hydrogen abstraction in different solvents are obtained directly from the slopes of the linear plots according to eq 4 (Table 1). Kinetic analysis, under pseudo-first-order reaction conditions were discussed in previous work,<sup>8</sup> and an example will be illustrated later in this contribution (vide infra).

The kinetic data in Table 1 shows important kinetic solvent effects. A change from hexane to acetonitrile causes the rate constants to decrease by a factor of  $\sim 12$  and  $\sim 35$  for *tert*-butoxyl and nitroxyl radicals, respectively.

Interestingly, and similar to the reported example of vitamin E, we observe that the rate constant is slower when the hydrogen bond acceptor (HBA) properties of the solvent increase ( $\beta_2^{\text{H}}$ ). In fact, there is a good correlation between *tert*-butoxyl radical hydrogen transfer rates for **1** with data previously reported for vitamin E,<sup>4</sup> Figure 1. This result shows a reactivity 100 times higher for vitamin E than **1** in any of the solvents employed. This suggests that *tert*-butoxyl radical reactivity is hindered by solvent molecules hydrogen-bonded to the substrate; the large effect would be unprecedented for hydrogen transfer from a C–H bond (vide infra),<sup>9</sup> but would be reasonable for reactions involving an OH site. Methanol was not examined as a solvent because *tert*-butoxyl radicals abstract hydrogen atoms from this solvent.<sup>10</sup>

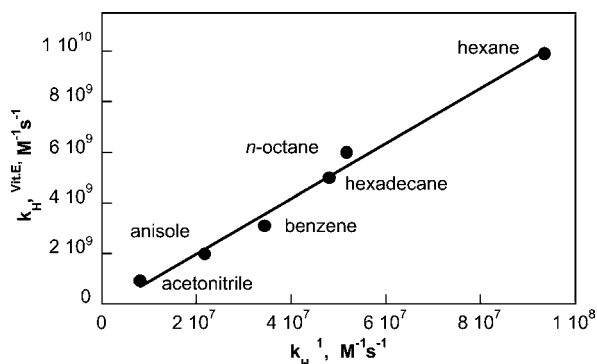
Similar behavior is observed in the case of the nitroxyl probe in hydrogen abstraction reactions; the rate constant decreases significantly on changing the solvent from hexane to methanol, although in this case we see unusually high

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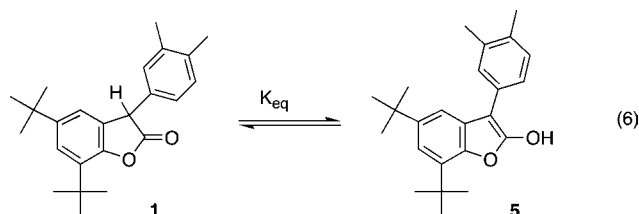
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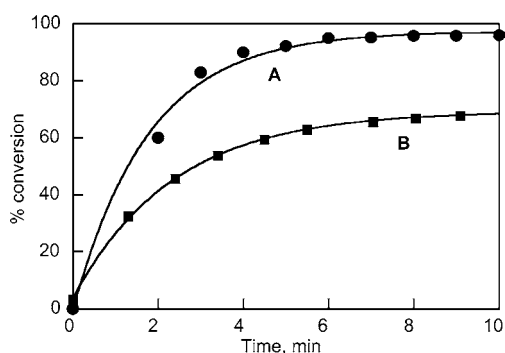
**Figure 1.** Rate constants for *tert*-butoxyl radical hydrogen abstraction from vitamin E,<sup>4</sup> plotted against the rate constants measured in this work for **1**, in several solvents at room temperature.

rate constants in light hydrocarbons. The rate constant observed in methanol is higher than in non-hydroxylic solvents. This behavior of nitroxyl radicals has been previously related with an interaction between the nitroxyl and the hydrogen bond donor property of the solvent.<sup>11</sup>

The results suggest that, just as in the case of phenols, the reactive species is the free hydroxyl form of the substrate, in other words the enol form of **1**, reaction 6.



If the equilibrium of reaction 6 is important, as suggested by the results, one would expect H/D exchange to be readily observable by NMR spectroscopy. This is indeed the case; Figure 2 shows the exchange as a function of time for 0.07

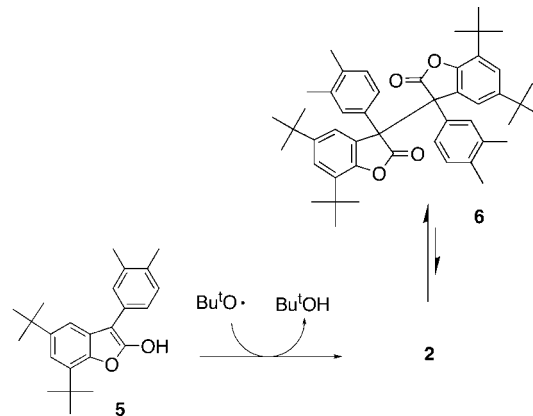


**Figure 2.** Percentage of the <sup>1</sup>H exchange based on the NMR signal followed at 4.2 ppm by adding a small amount of D<sub>2</sub>O in acetonitrile-*d*<sub>3</sub>. D<sub>2</sub>O concentration: (A) 0.73 M; (B) 0.07 M.

and 0.73 M water in acetonitrile-*d*<sub>3</sub>. The exchange occurs with a lifetime of about 2 min and is largely independent of the concentration of D<sub>2</sub>O, except for the percent exchange achieved in the plateau region. This means that 90% the exchange allowed at equilibrium is reached in 5–6 min. In contrast, when we carry out laser flash photolysis experiments under the same conditions we find that 90% of the decrease in rate constant for *tert*-butoxyl radicals (only about 30–35% decrease) is achieved within 30 s.<sup>12</sup> This suggests that the hydrogen donor species exchanges H-for-D much faster than the C–H/C–D exchange monitored by NMR; again, this is consistent with the O–H group in **5** as the hydrogen donor, but not with the C–H bond in **1** as a donor. The enol, while significantly less abundant than the keto form clearly dominates the reactivity patterns.

Several unusual observations in the data are easily explained if one assumes that the correct mechanism involves hydrogen abstraction from **5**, not from **1**. First, the excellent correlation of Figure 1 suggests a similar reactive species; further, the fact that *tert*-butoxyl reaction in hexane is about twice as fast as in octane is consistent with a near-diffusion controlled reaction, that is directly influenced by changes in the solvent viscosity. The viscosities of hexane, heptane, octane and hexadecane at 20 °C are 0.33, 0.41, 0.54, and 3.34 cP, respectively. The light hydrocarbons follow an excellent trend with viscosity. It is possible that in the case of hexadecane its effective viscosity is significantly influenced by the presence of di-*tert*-butyl peroxide in the mixture. Further, the small isotope effect observed ( $\leq 1.5$ ) is consistent with a very fast reaction, where selectivity is largely lost. If we assume the actual rate constant for abstraction from free enol **5** to be around  $10^{10} \text{ M}^{-1} \text{ s}^{-1}$  (i.e., close to diffusion controlled), then, the amount of enol in equilibrium at room temperature in nonpolar solvents is about 0.5% of the concentration of **1** (i.e.,  $K_{\text{eq}} \sim 0.005$ ), Scheme 3. Radical **2** is known to

**Scheme 3.** Hydrogen Abstraction from **5** by *tert*-Butoxyl Radicals and Dimerization of the Radicals

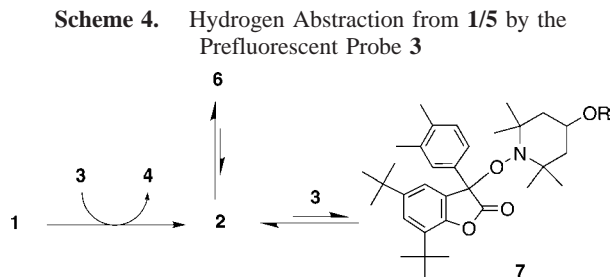


form the corresponding dimer, with a weak C–C bond that dissociates readily thermally.<sup>13</sup> The correlation of Figure 1

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is consistent with an enol-mediated reaction; we were surprised by the quality of the correlation, since the fraction of enol formed must change with the solvent. Most likely the enol concentration also correlates reasonably well with the hydrogen bond acceptor properties of the solvent ( $\beta_2^H$ ).

The rate constants for nitroxyl radical reaction with **1** in light hydrocarbons are about four times what could be predicted by extrapolating the data in other solvents, when the data are plotted against  $\beta_2^H$ . This may be due in part to the trapping of the radical by **3** in nonpolar solvents, according to Scheme 4. While our evidence for **7** is



inconclusive, its formation in nonpolar solvents may explain the increase in rate constant. It should also be noted that while the hydrocarbon solvents are not hydrogen bond acceptors, the probe itself may play to some degree this role, despite its low concentration.<sup>14</sup> Nitroxyl radicals also show significant solvent effects, at least in their trapping of carbon-centered radicals.<sup>15</sup>

The fast exchange observed in polar solvents is consistent with the presence of significant enol concentration in these solvents which is reflected in the rate constant (major interaction with HBA solvents). The strong solvent effect dependence among the solvents employed shows that the enol form is the reactive species in agreement with the behavior observed for phenolic compounds.<sup>3,16</sup>

The conclusion that the hydrogen donor is **5** rather than **1** led us to explore if hydrogen transfer could be mediated by electron transfer (i.e., electron transfer from the enol anion followed by protonation), as has been established to occur with DPPH (another common probe) in alcoholic solvents.<sup>11</sup> This was done by monitoring the progress of reaction 5 according to eq 4, for methanol and methanol-*O-d* in the

(12) This corresponds to an H/D isotope effect of  $\leq 1.5$ . The reactive species clearly is formed without requiring that the C–H/C–D exchange be complete. Unfortunately, it is virtually impossible to carry out laser experiments in less than 30 s following D<sub>2</sub>O addition.

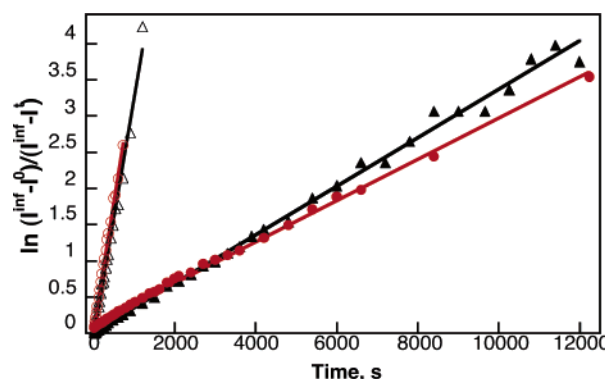
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(14) Product **7** is expected to be rather unstable and if formed does not survive chromatographic analysis. Further, the concentrations of probe used are too low for NMR analysis. At high concentration dimer **6** is the final product.

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absence and presence of 1% acetic acid (CH<sub>3</sub>COOD when appropriate), as shown in Figure 3. The large isotope effect



**Figure 3.** Reaction of **3** with **1** in methanol ( $\Delta$ ), methanol-*O-d* ( $\bullet$ ), in methanol containing 1% acetic acid (red  $\circ$ ), and in methanol-*O-d* containing 1% CH<sub>3</sub>COOD (red  $\bullet$ ). Plotted according to eq 4.

( $\sim 10$ , see Table 1) and the absence of any significant effect by addition of acetic acid<sup>11,17</sup> is consistent with a mechanism involving simple hydrogen abstraction from enol **5**.

Some earlier observations of substituent dependence of the reaction of alkoxyl radicals with lactones may now be easier to explain.<sup>5</sup> For example, replacement of the aryl substituent on the lactone ring leads to a significant increase in the rate constant for hydrogen abstraction, which was not easily explained before; it now appears likely that the observed increase in rate constant may result from changes in the abundance of the enol form.

In conclusion, our results show that the dominant hydrogen donor in the case of **1** is not the lactone commercialized as HP-136, but rather the enol form in equilibrium with the lactone, in this way making it analogous to many phenolic antioxidants where the H-donor is the OH group. In effect, the lactone form is not an antioxidant, but rather its enol is. Despite this, once the hydrogen transfer has occurred, the radical (**2**) behaves predominantly as a carbon centered radical, but with little or no reactivity toward oxygen.

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**Supporting Information Available:** Experimental procedures and additional details of kinetic studies by laser flash photolysis. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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