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Modeling the Co-Antioxidant Behavior of Monofunctional Phenols. Applications to Some Relevant Compounds

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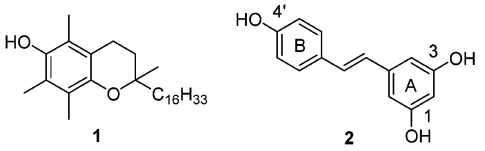
A study on the regeneration of α-tocopherol (vitamin E) by phenolic co-antioxidants in homogeneous hydrocarbon solution is reported. The behavior of some relevant phenols such as BHA, BHT, and *trans*-resveratrol appears to be nicely predicted by a model based on the knowledge of kinetic and thermochemical data concerning the various reactants. Despite its good reputation as an antioxidant, *trans*-resveratrol was found only moderately effective ($k_{inh} = 2.0 \times 10^5$ M^{-1} s^{-1} in chlorobenzene at 303 K) and unable to recycle vitamin E.

Resveratrol is a naturally occurring phenol, particularly abundant in grapes[1] and red wine.[2] Because red wine consumers in France have a lower than expected incidence of cardiovascular diseases,[3] the "French Paradox", a considerable number of investigations have been devoted to understanding the cardiovascular protective activity of red wine. The general consensus is that this is due to the antioxidant properties of the phenolic and polyphenolic constituents present in grapes' skin.[4] Early investigations suggested that *trans*-resveratrol was the principal agent responsible for the French Paradox, which has prompted massive examples of scientific literature describing its antioxidant properties. Notably, some of these reports attribute to *trans*-resveratrol an antioxidant activity comparable to (or even higher than) α-tocopherol (**1**),[5] nature's most effective lipid-soluble chain-breaking antioxidant,[6] while others indicate that *trans*-resveratrol is the main contributor to the total antioxidant power of red wine despite the fact that it may not be the most abundant phenol in wine.[7] *trans*-Resveratrol (**2**) has also been found to protect blood platelets from oxidative stress at concentrations 1000 times lower than ascorbic acid (vitamin C).[8]



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Despite the great interest in resveratrol as an antioxidant, the majority of investigations have relied on indirect methods to assess its antioxidant activity, and no kinetic data have been reported regarding its reactivity toward peroxyl radicals, the key feature for chain-breaking antioxidant activity. DFT calculations suggest that the mechanism of reaction of **2** with chain-propagating peroxyl radicals is hydrogen-atom transfer,[9] the rate of which depends to some extent on the O−H bond dissociation enthalpy (BDE).[10] Due to delocalization of the unpaired electron on both the A and B rings,[9] the phenoxyl radical arising from hydrogen abstraction from the 4′-OH group will be significantly more stabilized than the corresponding aryloxyl radicals obtained by abstraction from the hydroxyl groups in position 1 or 3, as also predicted by DFT calculations.[11] Since the BDE value for the 4′ hydroxyl is expected to be significantly lower than for 1- and 3-hydroxyl groups, *trans*-resveratrol can be regarded, to a first approximation, as a monofunctional phenol. Since the calculated 4′-OH BDE for *trans*-resveratrol is about 3.1 kcal/mol higher than that of α-tocopherol,[9] its reported extraordinary antioxidant activity is surprising. One possible explanation of resveratrol's radical scavenging ability in vivo and in crude plant extracts is that it acts synergistically with other antioxidants, as recently claimed by Liu and co-workers.[12] These authors reported that the strong antioxidant activity of resveratrol and some of its derivatives in

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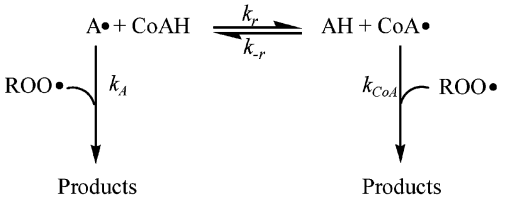
SCHEME 1

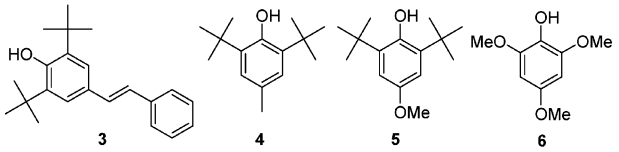


micelles arises from its ability to regenerate α-tocopherol.

We have recently proposed a quantitative model rationalizing regeneration among antioxidants.[13] This model, which is based on kinetic and thermochemical data concerning the reactants involved in the potential regeneration reactions, has been satisfactorily applied to the regeneration of α-tocopherol in homogeneous solution.

It has been shown (see Scheme 1) that a co-antioxidant (CoAH) may effectively recycle vitamin E (AH) when the O−H bond dissociation enthalpy (BDE) for CoAH is lower, or at least comparable to that of AH, provided the rate constant for regeneration, k_r, is at least 10^3 M^{-1} s^{-1} and that the rate constants for the reactions of peroxyl radicals, ROO•, with A• and CoA• are similar.

Resveratrol constitutes an excellent compound to further test this general model of regeneration among monofunctional phenols. We have also extended the investigation to 2,6-di-*tert*-butyl-4-styrylphenol (**3**, a synthetic hydroxystilbene) and to three phenols commonly used as antioxidants and co-antioxidants: 2,6-di-*tert*-butyl-4-methylphenol (**4**, BHT), 2,6-di-*tert*-butyl-4-methoxyphenol (**5**, BHA), and 2,4,6-trimethoxyphenol (**6**).



Results and Discussion

Controlled Autoxidation Studies. The autoxidation of a substrate initiated at a constant rate, R_i, by the thermal decomposition of an azo compound and containing a specific concentration of α-tocopherol gives an induction period whose duration is denoted as τ_0. Under the same conditions but with the simultaneous addition of a co-antioxidant capable of regenerating α-TOH from the corresponding α-tocopheroxyl radical, the reaction will have an induction period, τ, as given by eq 1[13]

$$\tau = \tau_0 + \tau_0\alpha\frac{[\text{CoAH}]}{[\alpha\text{-TOH}]} \quad (1)$$

$$\alpha = K_r\frac{k_{CoA}}{k_A} \quad (2)$$

where α is the regeneration coefficient (eq 2) whose value may lie between 0 (no regeneration) and 1 (complete regeneration).

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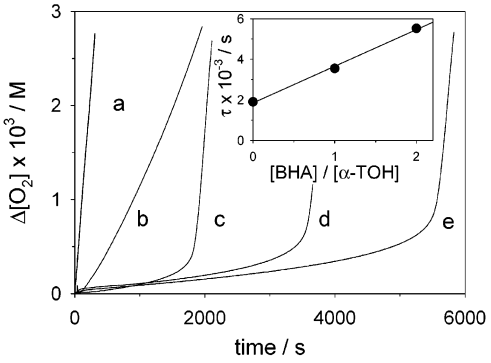

FIGURE 1. Oxygen consumption traces recorded at 30 °C during the autoxidation of styrene 7.5 M initiated by AMVN (5×10^{-2} M), in the absence of any antioxidant (a) and in the presence of the following: (b) 5.0×10^{-5} BHA; (c) 5.0×10^{-5} M α-TOH; (d) 5.0×10^{-5} M α-TOH and 5.0×10^{-5} BHA; (e) 5.0×10^{-5} M α-TOH and 1.0×10^{-4} BHA. The inset reports the length of the induction period as a function of the concentration ratio of the two antioxidants.

K_r can be estimated from the difference between the bond dissociation enthalpies (BDE) of the two equilibrating antioxidants, ΔBDE = BDE(CoAH) − BDE(α-TOH). Because the entropy change, Δ*S*, of the hydrogen atom exchange is negligible,[14] eq 3 holds.

$$-RT\ln K_r = \Delta G \approx \Delta\text{BDE} \quad (3)$$

An important condition for the recycling of α-TOH is that the two antioxidants and the corresponding radicals are in equilibrium, i.e., that the hydrogen exchange is faster than the combination of α-TO• with peroxyl radicals, this being true when eq 4 is satisfied.[13]

$$[\text{CoAH}] \geq (k_A/k_r)[\text{ROO}^\bullet] \quad (4)$$

The peroxyl radical concentration can be determined by eq 5,[15] where k_{inh} is the rate constant for the reaction of α-TOH with ROO•.

$$[\text{ROO}^\bullet] \approx R_i/(2k_{inh}[\alpha\text{-TOH}]) \quad (5)$$

In a typical autoxidation experiment,[16] eq 4 holds if $k_r \geq 3 \times 10^3$ M^{-1} s^{-1}. It is therefore important to know the value of k_r since the experimental regeneration coefficient will be lower than the value predicted by eq 2, if this constant is too small. The experimental value of α can be obtained by plotting τ against the ratio [CoAH]/[α-TOH]; intercept = τ_0, slope = $\tau_0\alpha$.

BHA (**5**) is a relatively poor antioxidant able only to retard the autoxidation of styrene initiated by AMVN at 30 °C in chlorobenzene (Figure 1). The rate constant for reaction of BHA with peroxyl radicals was determined by analyzing the autoxidation trace by the equation developed by Denisov.[17] The value obtained, viz., k_{inh} = 1.2×10^5 M^{-1} s^{-1}, is in excellent agreement with previous

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(15) Equation 5 is the simplified form of a more complete equation reported in ref 13 and is obtained assuming that the reaction of the co-antioxidant with peroxyl radicals is negligible with respect to that of α-TOH.

(16) $R_i = 5 \times 10^{-9}$ M s^{-1}; $k_{inh\ \alpha-TOH} = 3.2 \times 10^6$ M^{-1} s^{-1}; $k_A = 1 \times 10^8$ M^{-1} s^{-1}.

TABLE 1. Thermochemical and Kinetic Parameters for the Investigated Phenolic Antioxidants Measured in Benzene at 298 K unless Otherwise Noted

antioxidant	BDE (kcal M^{-1})	k_{inh}[d] (M^{-1} s^{-1})	ΔBDE[e] (kcal M^{-1})	K_r	α exptl[f]
1	78.2 ± 0.3[b]	3.2×10^6			
2	83.7[a]	2.0×10^5	+5.5	9×10^{-5}	0
3	78.9 ± 0.2[c]	2.7×10^4	+0.7	0.3	0.70
4	81.0 ± 0.1[b]	8.2×10^3	+2.8	9×10^{-3}	0
5	78.3 ± 0.1[b]	1.2×10^5	+0.1	~1	1
6	80.0 ± 0.1[b]	2.3×10^5	+1.8	0.05	0

[a] Estimated using the group additivity rule[20] under the assumption that the contribution of a *p*-3,5-dihydroxystyryl substituent is the same as that of a *p*-styryl substituent. [b] Reference 10. [c] Reference 20. [d] Measured in chlorobenzene, for these values the standard error is approximately 10%. [e] BDE(CoAH) − BDE(α-TOH). [f] The regeneration coefficient α refers to systems α-TOH/co-antioxidant.

data.[18] When α-TOH was added to the system, BHA became a very good inhibitor (Figure 1, traces d−e), that completely recycled α-tocopherol; the regeneration coefficient α was ca. 1 (Figure 1, inset).

Because the O−H BDE values for BHA and α-TOH are almost identical (see Table 1), the equilibrium constant for the regeneration reaction K_r is equal to 1. Since the experimental condition requiring fast equilibration for the hydrogen exchange reaction is guaranteed by the k_r value of 5.9×10^3 M^{-1} s^{-1}, determined in the separate experiments reported below, the rate constant ratio k_{CoA}/k_A is also close to 1.

Both BHT (**4**) and 2,4,6-trimethoxyphenol (**6**) are moderately active chain-breaking antioxidants able to retard thermally initiated (AMVN) styrene autoxidation but not giving a sharply defined inhibition period. Their rate constants for peroxyl radical trapping, measured by the method reported by Darley-Usmar and co-workers,[19] are 8.2×10^3 M^{-1} s^{-1} (**4**) and 2.3×10^5 M^{-1} s^{-1} (**6**), and their O−H BDE values are 81.0 and 80.0 kcal/mol, respectively. Unlike BHA (**5**), neither **4** nor **6** was able to regenerate α-tocopherol (**1**) when they were mixed with equimolar quantities of α-TOH (α = 0). At the end of the inhibited period, when α-tocopherol was completely consumed, the oxygen uptake was still mildly retarded due to presence of the co-antioxidant. This behavior can be simply explained in terms of eq 2 by considering that the K_r values of ca. 0 and 0.05 (estimated for **4** and **6**, respectively, from the ΔBDE differences reported in Table 1) are too small to give regeneration of α-TOH (Figure 2).

Despite being considered a very good antioxidant, resveratrol (**2**) behaves in homogeneous solution as a mild retarder of the thermally initiated autoxidation of styrene (Figure 3). Its rate constant for the reaction with peroxyl radical in chlorobenzene at 30 °C, $k_{inh} = 2.0 \times 10^5$ M^{-1} s^{-1}, obtained as already described,[19] is about 16 times lower than that of α-TOH (Table 1). Its lower reactivity,

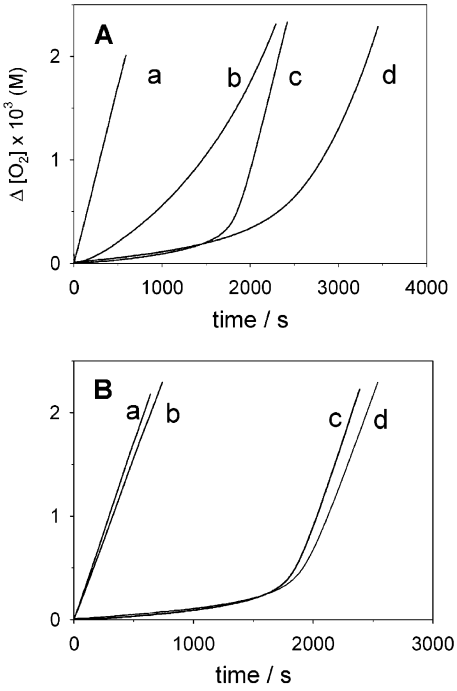

FIGURE 2. (A) Oxygen consumption traces recorded during the autoxidation of styrene 7.5 M at 30 °C initiated by AMVN (5×10^{-3} M) in the absence of any antioxidant (a) and in the presence of the following: (b) 2,4,6-trimethoxyphenol 5.0×10^{-6} M; (c) α-TOH 5.0×10^{-6} M; (d) α-TOH and 2,4,6-trimethoxyphenol both 5.0×10^{-6} M. (B) Oxygen consumption traces recorded during the autoxidation of styrene 7.5 M at 30 °C initiated by AMVN (5×10^{-3} M) in the absence of any antioxidant (a) and in the presence of the following: (b) BHT 5.0×10^{-6} M; (c) α-TOH 5.0×10^{-6} M; (d) α-TOH and BHT both 5.0×10^{-6} M.

however, is not completely unexpected in view of its O−H BDE value, which is predicted by DFT calculations[9] to be 3.1 kcal/mol higher than that of α-TOH. An experimental BDE value for **2** is not yet available but can be estimated with reasonable accuracy by using the group additivity rule.[10,20] With the assumption that the contribution of a *p*-3,5-dihydroxystyryl substituent is the same as that of a *p*-styryl substituent, a BDE = 83.7 kcal/mol is obtained for the 4′ hydroxyl group. Considering the large BDE difference between **2** and α-tocopherol (+5.5 kcal/mol), K_r is predicted to be 9.2×10^{-5}, and assuming that the ratio k_{CoA}/k_A is nearly 1 (as is observed for **5**, vide supra), the resulting regeneration coefficient α would be negligible, i.e., no regeneration of α-tocopherol from **2** should be expected. This is, indeed, the case since Figure 3A reveals that the inhibition of styrene autoxidation by mixtures of **2** and α-TOH (**1**) is simply the sum of individual effects and synergism does not occur.

We have also studied the antioxidant behavior of mixtures of resveratrol (**2**) and BHT (**4**) because **4** has an O−H BDE value (81.0 kcal/mol)[14] which is 2.7 kcal/mol below that estimated for **2** (vide supra), corresponding to a $K_r \approx 96$. This would imply that BHT (**4**), although significantly less reactive than resveratrol (**2**) toward peroxyl radicals (see Table 1) could quantitatively regenerate **2** from the corresponding phenoxyl radical. Figure

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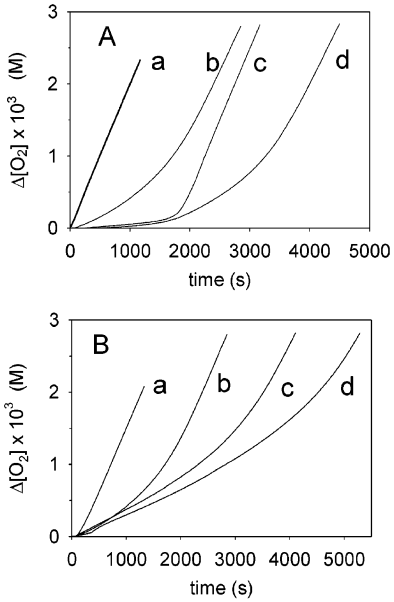
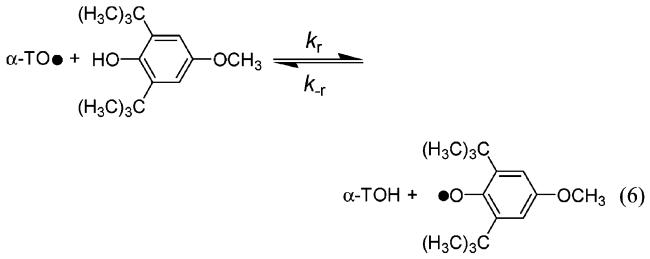


FIGURE 3. (A) Oxygen consumption traces recorded during the autoxidation of styrene 4.3 M at 30 °C initiated by AMVN (5.0×10^{-3} M) in the absence of any antioxidant (a) and in the presence of the following: (b) resveratrol 5.0×10^{-6} M; (c) α-TOH 5.0×10^{-6} M; (d) α-TOH and resveratrol both 5.0×10^{-6} M. **(**B) Oxygen consumption traces recorded during the autoxidation of styrene 4.3 M at 30 °C initiated by AMVN (5.0×10^{-3} M) in the presence of the following: (a) BHT 5.0×10^{-6} M; (b) resveratrol 5.0×10^{-6} M; (c) resveratrol and BHT both 5.0×10^{-6} M; (d) resveratrol 5.0×10^{-6} M and BHT 1.0×10^{-5} M.

3B shows that resveratrol (plot b) is more effective in inhibiting the autoxidation of styrene than BHT alone (plot a) although neither of these antioxidants gave well-defined inhibition periods. With 1:1 and 1:2 resveratrol/BHT mixtures the oxygen uptake traces were the same as those produced by doubling and tripling the concentration of (**2**) (plots c and d). This indicates that BHT is regenerating resveratrol. The efficiency of regeneration, obtained by simulating the experimental autoxidation plots by a stochastic method previously described,[13] provides an α value of 1 (100% regeneration), as would be predicted by eq 3.

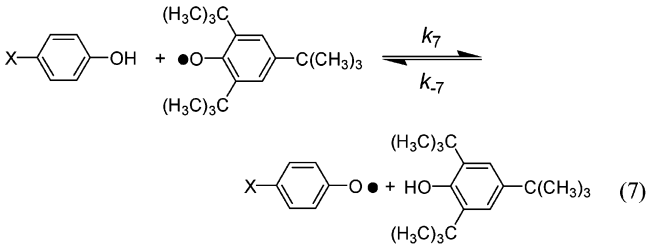
To stress the importance of ΔBDE as the primary factor governing regeneration among monophenolic antioxidants, we have investigated the antioxidant behavior of mixtures of α-TOH (**1**) and 2,6-di-*tert*-butyl-4-styrylphenol (**3**). The latter is structurally related to resveratrol and has an experimental O−H BDE of 78.9 kcal/mol,[20] i.e., 4.8 kcal/mol lower than **2**. The rate constant for the trapping of peroxyl radicals by **3** was determined[19] as 2.7×10^4 M^{-1} s^{-1}. As shown in Figure S1, compound **3** regenerates α-TOH with good efficiency ($\alpha = 0.7$, see inset), despite the fact that its antioxidant activity is lower than that for **6**. This value is higher than the efficiency predicted by eq 3 considering the ΔBDE between **1** and **3** (+0.7 kcal/mol, corresponding to $K_r = 0.3$) and assuming a ratio $k_{CoA}/k_A = 1$. Indeed, according to eq 2, a value $\alpha = 0.7$ requires that $k_{CoA}/k_A = 2.3$, i.e., that the phenoxyl radical from **3** reacts with peroxyl radicals about twice as fast as the tocopheroxyl radical. Although no experimental data are available on the rate of radical−radical combination between the phenoxyl radical from **3** and peroxyl radicals, the higher reactivity of CoA• with respect of the α-tocopheroxyl radical may possibly be due to the fact that the unpaired electron is delocalized into the styryl substituent of CoA•, so that additional modes of attack by peroxyl radicals are possible.

Determination of the Regeneration Rate Constants, k_r. The rate constant for regeneration of α-tocopherol by BHA (**5**) (eq 6) has been obtained in benzene solution at room temperature, by the kinetic EPR method previously described.[13] For convenience, we measured the



(6)

reverse rate constant k_{-r}, i.e., the rate for hydrogen atom transfer from α-tocopherol to the phenoxyl radical of **5**, from which k_r was obtained using the K_r value estimated from the known ΔBDE difference (Table 1). The method consisted in monitoring the decay of a spectral line of the very persistent 2,6-di-*tert*-butyl-4-methoxyphenoxyl radical, not superimposed to those of α-TO•, after a fast injection of a concentrated stock solution of α-TOH (final concentration ca. 1 mM) into the sample tube, while continuously bubbling with nitrogen to induce rapid mixing. Under the experimental conditions employed, the EPR signal decayed completely in approximately 5−10 s after the α-tocopherol injection, following good pseudo-first-order kinetics. The measured rate constant, k_{-r}, was 7.0×10^3 M^{-1} s^{-1} from which the value $k_r = 5.9 \times 10^3$ M^{-1} s^{-1} in benzene at 298 K was calculated using the difference of 0.1 kcal/mol between the BDE's of **5** and **1**. Attempts to measure the rate of reaction of resveratrol with α-tocopheroxyl radicals were unsuccessful due to limited solubility of **2** in benzene. Similarly, we could not measure the rate of regeneration of resveratrol by BHT (**4**). However, this value could be reliably estimated by combining our previous thermodynamic data[20] with the kinetic data reported by Mahoney and DaRooge in their pioneering work.[21] The rates for reaction of some 4-substituted phenols (XC_6H_4OH), with X= CH_3O, $(CH_3)_3C$, and H) with the phenoxyl radical from 2,4,6-tri-*tert*-butylphenol (**7**) (eq 7) were measured by stopped flow-kinetic EPR as 6.0×10^3, 1.1×10^2, 8.0 M^{-1} s^{-1} respectively.[21]



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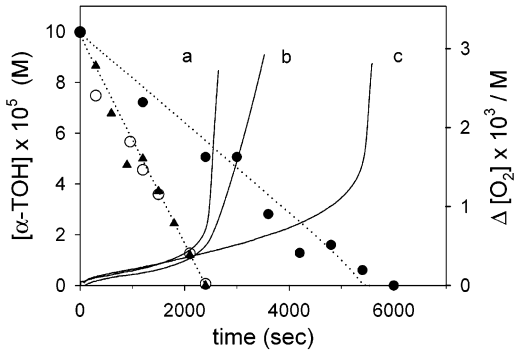

FIGURE 4. α-TOH consumptions observed from a 1×10^{-4} M chlorobenzene solution at 60 °C during the thermal decomposition of 5×10^{-3} M AIBN in the absence of co-antioxidant (○) and in the presence of 1×10^{-4} M resveratrol (▲) and 1×10^{-4} M BHA (●). The plot also shows the oxygen uptake traces obtained under similar conditions except for the presence of 4.3 M styrene (traces a, b, and c refer to the experiments carried out in the presence of only α-TOH, the mixture (1:1) α-TOH/resveratrol, and the mixture (1:1) α-TOH/BHA, respectively). Dotted lines show computer simulation of α-TOH consumption.

When the logarithm of the rate constants is plotted against the ΔBDE difference BDE(XC_6H_4OH) − BDE(**7**) an excellent linear correlation was obtained (Figure S2), similar to our previously reported plot in a closely related system.[13] The values for the BDE(XC_6H_4OH) are 82.8, 85.3, and 88.3 kcal/mol for X = MeO, Me_3C, and H, respectively,[20] and 81.2 kcal/mol for **7**,[22] affording the empirical correlation log $k_7 = 4.45 - 0.52$ (ΔBDE). By substituting in this equation the ΔBDE values for resveratrol, the value $k_7 = 1.5 \times 10^3$ M^{-1} s^{-1} is obtained which provides, together with ΔBDE, the rate constant for the reverse reaction $k_{-7} = 9.6 \times 10^4$ M^{-1} s^{-1}. Since 2,4,6-tri-*tert*-butylphenol (**7**) and BHT (**4**) have almost identical O−H BDE's and the same substituents *ortho* to the OH group, this value also represents a good estimate for the rate of regeneration of resveratrol (**2**) by BHT (**4**), i.e., $k_r \sim 9.6 \times 10^4$ M^{-1} s^{-1}, a result in agreement with the observed synergistic behavior of resveratrol/BHT co-antioxidant mixtures.

Product Studies. The complete regeneration of α-tocopherol by BHA (**5**) was confirmed by studying the time dependence of the concentrations of the two antioxidants, measured by HPLC-MS using electrospray ionization (ESI-MS), during the thermal decomposition of AIBN at 60 °C, i.e., under experimental conditions similar to those used when carrying out the autoxidation reactions. In these experiments no styrene was introduced to avoid interference with the phenol analytes in the ESI-MS analysis due to matrix effects, and the temperature was kept higher than 30 °C to accelerate the decomposition of the azo initiator. Matched autoxidation experiments performed in the presence of 4.3 M styrene (see Figure 4) showed induction periods identical to those obtained from the disappearance of α-TOH. The plots obtained in the presence of both antioxidants indicate that the lengthening of the induction period is due to a slower consumption of α-tocopherol. No retarding of α-TOH consumption was observed when resveratrol was used as the co-antioxidant and induction periods recorded during autoxidation in the presence or absence of reveratrol are almost superimposable (plot b). Simulations of the time dependence of the α-tocopherol consumption under the experimental conditions employed (see the Experimental Section) matched the experimental observations.

Conclusion

The general model we have recently proposed[13] can explain and predict synergistic behavior among monofunctional phenolic antioxidants. In general, the regeneration of an antioxidant AH by a co-antioxidant CoAH is possible when the rate constant, k_r, is 10^3 M^{-1} s^{-1} or higher and CoAH has an O−H BDE value lower or at least close to that of AH. When the ratio between the rate constants for the reaction of peroxyl radicals with the corresponding phenoxyl radicals k_{CoA}/k_A is ∼1, the above conditions are verified when the ΔBDE difference BDE(CoAH) − BDE(AH) is less than 1 kcal/mol.

Contrary to general belief, resveratrol in homogeneous solution is neither an outstanding antioxidant nor capable of effectively regenerating α-tocopherol. Indeed, other phenolic derivatives present in red wine might be more likely responsible for its antioxidant activity. Among them gallic acid and the numerous flavonoids containing the catechol ring which are characterized by low O−H BDE values due to intramolecular hydrogen bonding.[23] Whether the reported antioxidant and co-antioxidant virtues of resveratrol would manifest themselves only in heterogeneous systems and whether our model would be suited to describe autoxidations in such media will be a matter for further work.

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Supporting Information Available: Figures S1 and S2 and the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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