Reaction of Singlet-Excited 2,3-Diazabicyclo[2.2.2]oct-2-ene and *tert*-Butoxyl Radicals with Aryl-Substituted Benzofuranones

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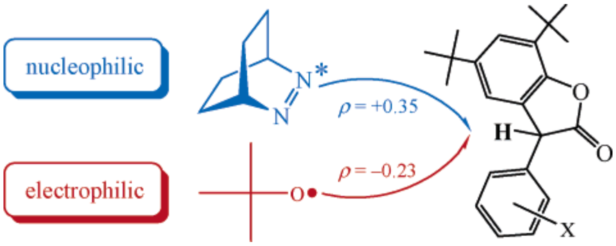

5,7-Di-*tert*-butyl-3-aryl-3*H*-benzofuran-2-ones are lactones with potential antioxidant activity, owing to their abstractable benzylic C−H hydrogens. The fluorescence quenching of the azoalkane 2,3-diazabicyclo-[2.2.2]oct-2-ene (DBO), an established probe for the hydrogen-donor propensity of chain-breaking antioxidants, was investigated for 16 aryl-substituted benzofuranone derivatives [*m*,*m*-$(CF_3)_2$, *p*-CN, *m*-CN, *p*-CF_3, *p*-$COOCH_3$, *m*-CF_3, *p*-Cl, *p*-F, H, *m*-CH_3, *p*-CH_3, *m*,*p*-$(CH_3)_2$, *p*-OCH_3, *o*-CH_3, *o*-CF_3, *o*,*m*-$(CH_3)_2$]. Analysis of the rate data in terms of a linear free energy relationship yielded a reaction constant of $\rho = +0.35$. This implies that n,π*-excited DBO acts as nucleophilic species. In contrast, hydrogen abstraction of *tert*-butoxyl radicals from the benzofuranones was accelerated by electron-donating substituents ($\rho = -0.23$), in conformity with the electrophilic character of oxygen-centered alkoxyl radicals. Possible implications for the optimization of the hydrogen-donor propensity of antioxidants through structural variation are discussed.

Introduction

Free radicals play a key role in the degradation processes of biological structures as well as polymer materials.[1] Photolytic or radiolytic processes may lead to the formation of carbon-centered radicals R$^\bullet$, for instance, by Norrish type-I cleavage of carbonyl-containing polymer backbones. The initially formed R$^\bullet$ react with oxygen to form peroxyl radicals, ROO$^\bullet$, which subsequently generate additional radicals by hydrogen abstraction. The propagation of the chain reaction, known as autoxidation, can be hindered by chain-breaking antioxidants that scavenge free radicals via hydrogen donation. As a result, the antioxidant is transformed into a less-reactive, often persistent radical, such that the autoxidative cycle is interrupted. Based on this mechanism, two essential key characteristics of a good chain-breaking antioxidant are a high efficiency to act as hydrogen donor and a high stability of the antioxidant-derived radical.

Nature relies heavily on phenolic antioxidants, for example, tocopherols protect living cell membranes from oxidative stress.[2] While such phenolic antioxidants have also found widespread use in the polymer industry, lactone-based antioxidants have become increasingly popular for polymer applications in recent years. These heterocycles, based on 3-aryl-3*H*-benzofuran-2-one, have labile benzylic C−H bonds and are, therefore, highly reactive in hydrogen-transfer processes.[3−5] They are presumed, in addition to the interception of oxygen-centered radicals, to

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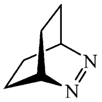
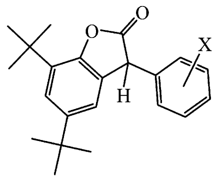
intercept also nucleophilic carbon-centered radicals.[6] Furthermore, the antioxidant radicals derived from hydrogen abstraction are very stable, as documented by their inertness toward reaction with oxygen.[4,5,7]

Triplet-excited ketones with n,π^* character, like benzophenone, and alkoxyl radicals as their ground-state analogues have been widely used to assess the hydrogen-donor reactivity of antioxidants by laser-flash photolysis.[4,5,7−14] However, spectral overlap between the reactive species (radical or triplet state) and the antioxidant itself or the antioxidant-derived radical limit a model-free direct kinetic data treatment as well as their routine use, for example, for screening assays. We have, therefore, introduced fluorescence quenching of the bicyclic azoalkane 2,3-diazabicyclo[2.2.2]oct-2-ene (DBO) for the evaluation of the hydrogen-donor reactivity of phenols (among them tocopherols), ascorbic acid, uric acid, and melanine-related dihydroxyindoles.[15−20] Most importantly, the monitoring by fluorescence allows direct detection of the reactive intermediate with the highest sensitivity and selectivity, which bypasses the above-mentioned complications as a result of spectral interferences. This becomes particularly important when the antioxidant is strongly absorbing (e.g., melanin)[15] or when reactions are monitored in heterogeneous environments. In fact, we have recently extended the fluorescence-based quenching by antioxidants to amphiphilic DBO derivatives to study interactions between membrane- or micelle-bound probes with water-soluble as well as lipid-soluble antioxidants.[16−18]



DBO



1-16

m,m-(CF$_3$)$_2$ (**1**)
p-CN (**2**)
m-CN (**3**)
p-CF$_3$ (**4**)
p-COOCH$_3$ (**5**)
m-CF$_3$ (**6**)
p-Cl (**7**)
p-F (**8**)

H (**9**)
m-CH$_3$ (**10**)
p-CH$_3$ (**11**)
m,p-(CH$_3$)$_2$ (**12**)
p-OCH$_3$ (**13**)
o-CH$_3$ (**14**)
o-CF$_3$ (**15**)
o,m-(CH$_3$)$_2$ (**16**)

In this study, we have investigated the relative hydrogen-donor propensities of a series of aryl-substituted 5,7-di-*tert*-butyl-3-aryl-3*H*-benzofuran-2-ones by using DBO as photophysical probe. For comparison, we also measured reaction rate constants with *tert*-butoxyl radicals, which can be assessed indirectly by monitoring the time-resolved rise in transient absorption of the lactone-derived radicals.[4,5,7] Besides its mechanistic implications, this study is relevant for the development of benzofuranones with improved hydrogen-donor activity.

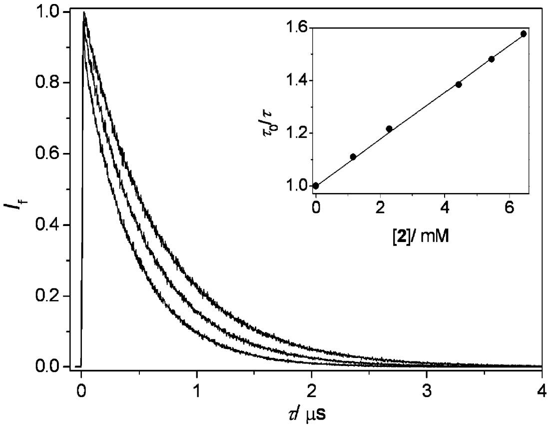


FIGURE 1. Time-resolved fluorescence quenching of DBO by **2** ([**2**] = 0, 2.28, and 5.45 mM) in degassed acetonitrile. The inset shows the corresponding kinetic Stern−Volmer plot.

Results

Fluorescence Quenching of DBO. Time-resolved fluorescence quenching experiments were performed in degassed acetonitrile solutions. Upon laser excitation at 355 nm, the typical broad fluorescence spectrum of DBO with a maximum at 430 nm was observed. The measured fluorescence lifetime in the absence of quencher (τ_0) was 690 ns.[21] Increasing the quencher concentration led to a shortening of the fluorescence lifetime (Figure 1). Data analysis (cf. inset of Figure 1) of the obtained lifetimes at different antioxidant concentrations by using kinetic equivalents of Stern−Volmer plots ($\tau_0/\tau = 1 + k_q\tau_0$[benzofuranone]) yielded the bimolecular quenching rate constants (k_q). These are compiled in Table 1 together with the corresponding Hammett substituent constants, σ.[22]

The rate constants, k_q, were in the range of 10^7−10^8 M^{-1} s^{-1}, about 1−2 orders of magnitude lower than those for phenolic antioxidants.[18−20] For comparison, toluene, which lacks the bisbenzylic substitution feature, reacts substantially slower, with a rate constant of 2.2×10^5 M^{-1} s^{-1} in acetonitrile.[20] Diphenylmethanol quenches the fluorescence of DBO with a rate constant of 2.6×10^7 M^{-1} s^{-1} in acetonitrile,[23] which is three times slower than the rate for the parent 5,7-di-*tert*-butyl-3-phenyl-3*H*-benzofuran-2-one (**9**). The slightly higher hydrogen-donor propensity of the 3-aryl-3*H*-benzofuran-2-ones relative to diphenylmethanol reflects presumably the extra stabilization of the resulting lactone-derived radical by spin delocalization on the carbonyl oxygen.[4,5]

The bimolecular quenching rate constants showed a significant dependence on the substitution pattern of the 3-aryl ring. For example, para substitution with the electron-withdrawing

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TABLE 1. Bimolecular Quenching Rate Constants for Singlet-excited DBO and *tert*-butoxyl Radicals by 3-aryl-3*H*-benzofuran-2-ones

	X	σ^a	k_q (10^7 M^{-1} s^{-1})			X	σ^a	k_q (10^7 M^{-1} s^{-1})	
			^{1}DBO^{*b}	t-BuO$^{\bullet c}$				^{1}DBO^{*b}	t-BuO$^{\bullet c}$
1	m,m-$(CF_3)_2$	0.86 ^{d}	15.0	0.31	**9**	H	0.00	7.1	0.41
2	p-CN	0.66	13.0	0.26	**10**	m-CH_3	−0.07	8.8	
3	m-CN	0.56	18.7		**11**	p-CH_3	−0.17	7.7	
4	p-CF_3	0.54	11.6		**12**	m,p-$(CH_3)_2$	−0.24^d	6.4	0.42
5	p-$COOCH_3$	0.45	10.9		**13**	p-OCH_3	−0.27	6.0	0.58
6	m-CF_3	0.43	10.2		**14**	o-CH_3		7.0	
7	p-Cl	0.23	12.7		**15**	o-CF_3		6.1	
8	p-F	0.06	8.8	0.50	**16**	o,m-$(CH_3)_2$		4.4	

[a] Substituent constant from ref 22. [b] Bimolecular fluorescence quenching rate constant of DBO in acetonitrile; 10% error. [c] Determined by laser-flash photolysis in acetonitrile/di-*tert*-butylperoxide (4/1); 20% error. [d] Calculated by the addition of the individual substituent constants.

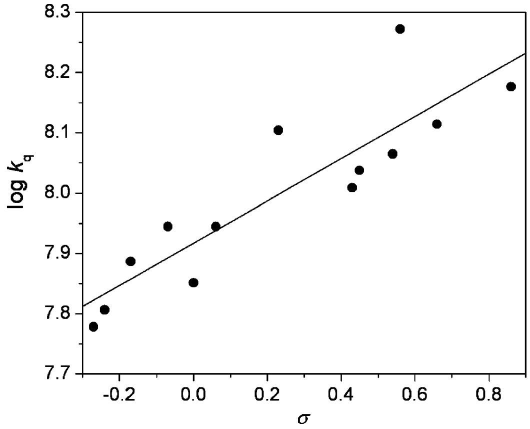

FIGURE 2. Hammett plot of the logarithmic DBO fluorescence quenching rate constants k_q versus the substituent constants σ for 3-aryl-3*H*-benzofuran-2-ones.

p-CN group (**2**) led to a two times higher rate constant compared to that of the derivative with the electron-donating p-OCH_3 group (**13**). A quantitative analysis of the obtained kinetic data by means of linear free energy relationships was performed for the derivatives with meta and para substituents. The ortho-substituted benzofuranones **14**−**16** were omitted because of possible steric hindrance effects.[24] Figure 2 shows the plot of the logarithmic quenching rate constants versus the Hammett substituent constants σ, according to the Hammett equation ($\log k_q = \log k_0 + \rho\sigma$), which yielded a satisfactory linear relation ($r = 0.886$, $n = 13$). Most important, the linear regression yielded a *positive* reaction constant ($\rho = +0.35$).

To illustrate solvent effects, the fluorescence quenching of DBO was also studied in n-hexane ($\tau_0 = 310$ ns) for the one-electron-acceptor-substituted **2** and the one-electron-donor-substituted **12** derivative. Rate constants of 1.2 and 0.36×10^9 M^{-1} s^{-1} were determined, respectively, corresponding to a reactivity enhancement by a factor of 9.2 and 5.6 in n-hexane. Deuterium kinetic isotope effects were determined for derivative **4** in wet acetonitrile. The H/D exchange of the benzylic C−H proton in the presence of D_2O was followed by the disappearance of its ^{1}H NMR signal at 5.0 ppm, which was complete within 2 h.[25] Quenching rate constants of 1.2 and 0.61×10^8 M^{-1} s^{-1} were determined in the presence of 2 M H_2O and D_2O, respectively, which corresponds to a deuterium isotope effect of 2.0. This isotope effect is smaller than that observed for alkylbenzenes, for example, $k_q(H)/k_q(D) = 5.9$ for 1,3,5-trimethylbenzene,[20] which is unquestionably due to the lower reactivity (factor 10−100) of the latter compared with the investigated 3-aryl-3*H*-benzofuran-2-ones (reactivity−selectivity principle). It is important to note that both the solvent and the deuterium isotope effect indicate a sizable *selectivity* in the fluorescence quenching and, therefore, in the hydrogen-atom abstraction step.

Reaction of *tert*-Butoxyl Radicals. Alternative methods to assess hydrogen-donor propensities of antioxidants by direct time-resolved transient absorption measurements, namely, the use of triplet-excited benzophenone or cumyloxyl radicals as probes, proved to be not readily applicable to benzofuranones, as a consequence of spectral overlap between the reactive species[26,27] and the lactone-derived radicals.[3−5,28] Scaiano and co-workers have introduced laser-flash photolysis studies (XeCl excimer laser excitation, $\lambda_{exc} = 308$ nm, $\lambda_{obs} = 340$ nm) of *tert*-butoxyl radicals as an indirect approach to determine the reactivity of benzofuranones by monitoring the time-resolved rise of the resulting lactone radicals, rather than the reactive species itself. The inertness of the *tert*-butoxyl and the lactone-derived radicals[4,5] toward oxygen allowed these experiments to be performed in air-equilibrated solutions.

The transient absorption spectra for three representative examples are shown in Figure 3, confirming the formation of carbon-centered lactone-derived radicals as primary intermediates of the hydrogen-atom transfer. The substitution pattern had a significant influence on the transient absorption spectra. The unsubstituted 5,7-di-*tert*-butyl-3-aryl-3*H*-benzofuran-2-one (**9**) showed a strong band at 330 nm and a weaker one at 530 nm. The spectrum of the *para*-methoxy-substituted derivative, **13**, was characterized by a strong band at 345 nm and a weaker, yet very broad band starting at 500 nm and extending to above 600 nm. The transient spectrum of the *para*-cyano-substituted derivative, **2**, displayed a strong absorption at 350 nm and weaker ones in the visible region. Generally, the UV bands of the spectra were very similar to those observed for benzylic radicals,[5,29] albeit the second band in the visible region was

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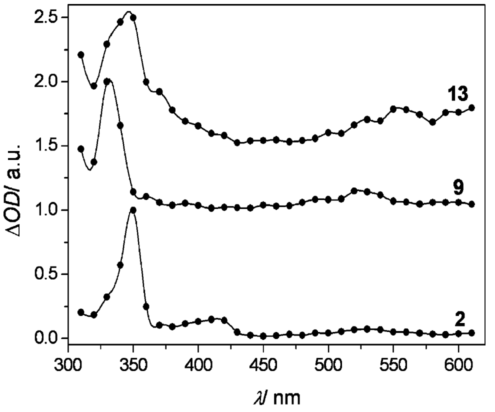

FIGURE 3. Transient absorption spectra (4−6 μs after laser flash) of the radicals derived from benzofuranones (40 mM each) in air-equilibrated acetonitrile/di-*tert*-butylperoxide (4/1).

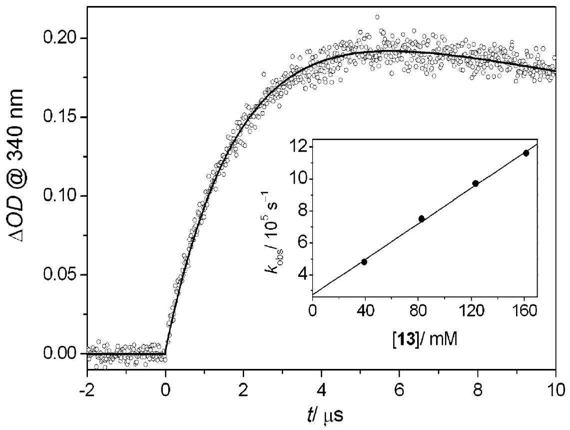

FIGURE 4. Transient absorption rise kinetics of the radicals derived from benzofuranone **13** (40 mM) in air-equilibrated acetonitrile/di-*tert*-butylperoxide (4/1). The fit (solid line) is based on a monoexponential rise and decay function. The inset shows the pertinent plot of the observed rate constants versus benzofuranone concentration.

stronger. This enhancement is commonly associated with the presence of heteroatoms.[5,29]

The observed reaction rates (k_{obs}) were obtained from the monoexponential rise kinetics and were plotted (Figure 4) against the antioxidant concentration according to $k_{obs} = k_0 + k_q$[benzofuranone] to afford the bimolecular rate constants (k_q) for hydrogen abstraction by *tert*-butoxyl radicals (cf. Table 1). The intercept yielded the apparent rate constant $k_0 = 1/\tau_0$ for the decay rate of *tert*-butoxyl radicals in the absence of a scavenger under the selected conditions [acetonitrile/di-*tert*-butylperoxide (4/1)]. The extracted lifetime corresponded to 3.4 μs, which compares well with the data in earlier reports, for example, 1.8 μs in benzene/di-*tert*-butylperoxide (1/2).[30]

The measurements for *tert*-butoxyl radicals were only performed for two strongly electron-withdrawing substituents (**1** and **2**), two electronically "neutral" substituents (**8** and **9**), and two strongly electron-donating substituents (**12** and **13**), because the variation in the rate constants in dependence on the aryl substitution turned out to be small in relation to the larger error of the transient absorption method. The bimolecular rate constants were about 10^6 M^{-1} s^{-1}, 2−3 orders of magnitude lower than that observed for phenolic antioxidants.[18−20] In comparison, rate constants for the hydrogen abstractions of *tert*-butoxyl radicals from alkylbenzenes are 2.3×10^5 M^{-1} s^{-1} for toluene and 6.9×10^6 M^{-1} s^{-1} for diphenylmethanol, both in benzene/di-*tert*-butylperoxide (1/2) as solvent.[30] This suggests that the investigated benzofuranones are substantially more reactive than simple alkylbenzenes, yet equally or somewhat more reactive than diphenylmethanol. This reactivity pattern resembles, therefore, that observed for singlet-excited DBO (see above). However, the fine-tuning within a closely related series of structurally identical but electronically different, namely, aryl-substituted homologues is distinct: in contrast to the observations made for singlet-excited DBO, hydrogen abstraction was accelerated by electron-donating substituents, which was also borne out by a negative reaction constant ($\rho = -0.23$) of the Hammett plot ($r = 0.853$, $n = 6$).

Solvent and deuterium isotope effects in the reaction of *tert*-butoxyl radicals with compound **12** were reported previously.[7] The reaction was accelerated in nonpolar solvents. Deuterium isotope effects in acetonitrile were also found to be significant (1.4−1.5). These reactivity data compare well with those presently measured for singlet-excited DBO (see above).

Discussion

Peroxyl radicals and their carbon-centered radical precursors are the most relevant reactive species involved in autoxidation processes. However, the time-resolved direct monitoring of their scavenging reactions with antioxidants is challenging from a spectroscopic point of view. Alternatively, *tert*-butoxyl radicals[4,5,7,8,11−13,20] and, more recently, fluorescent DBO[18−20,23,31−36] have been demonstrated to react with chain-breaking antioxidants by hydrogen-atom abstraction and have been employed as kinetic probes to assess their hydrogen-donor propensity by transient absorption or emission techniques. The presently investigated 3-aryl-3*H*-benzofuran-2-ones are structurally closely related to methylbenzenes and especially diphenylmethanol, for which hydrogen-atom abstraction has been previously established as a quenching mechanism.[20,23] This is further supported by the observation of significant deuterium isotope effects (cf. Results). The present reactivity data for (*i*) quenching of singlet-excited DBO and (*ii*) scavenging of *tert*-butoxyl radicals are, therefore, interpreted in terms of hydrogen-atom abstraction as the common primary reaction mechanism.[37]

Generally speaking, the rate of hydrogen-atom abstraction depends on the reaction thermodynamics, in particular, on the bond dissociation energy (BDE) of the abstractable hydrogen and on the philicity of the abstracting species. The influence of philicity is also known as the "polar effect" in hydrogen-abstraction reactions, which has been discussed for several n,π*-excited chromophores, that is, ketones and azoalkanes, as well as alkoxyl radicals.[8,9,20,34−36,38−40] For *tert*-butoxyl and *tert*-butyl radicals, in particular, there is comprehensive evidence that the thermodynamics is important but that the philicity of the radical

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also gives rise to a distinctive reactivity pattern.[38,41] Kinetic studies on hydrogen abstractions with aryl-substituted toluenes in haloalkanes at 323 K afforded a negative Hammett reaction constant for *tert*-butoxyl radicals ($\rho = -0.41$),[38] which demonstrates that this reactive intermediate behaves as an *electrophilic* species. In addition, *tert*-butoxyl radicals, as well as their excited-state analogues, excited ketones, for example, triplet benzophenone, have a high preference for the abstraction of nucleophilic hydrogens, namely, α C−H in alkanes, ethers, alcohols, and amines[36,42−44] but are reluctant toward abstraction from electrophilic C−H hydrogens, for example, from acetonitrile or chloroform. Not surprisingly, the present reactivity data on benzylic C−H hydrogen-atom abstraction from the aryl-substituted benzofuranones **1**, **2**, **8**, **9**, **12**, and **13** revealed a negative reaction rate constant as well ($\rho = -0.23$ in acetonitrile, cf. Results), which is fully in line with the electrophilic reactivity of this alkoxyl radical. However, it is not entirely clear whether the hydrogens in these benzofuranones should be qualified as being nucleophilic in nature, because the adjacent carbonyl group will transfer at least a partial electrophilicity, akin to the situation of the cyano group in acetonitrile. In fact, it has been suggested that the benzofuranones are also capable of intercepting (nucleophilic) carbon-centered radicals.[6]

Kinetic measurements on the reaction of singlet-excited DBO with various antioxidants,[15−19] phenols,[20] and alkylbenzenes[20] have demonstrated that the BDE is a very important factor in determining the reaction rates for hydrogen abstraction. This has been previously employed to assess the relative hydrogen-donor propensities of structurally related antioxidants, for example, for α, β, γ, and δ tocopherols.[18] However, the philicity of singlet-excited DBO has remained under debate. On one hand, singlet-excited DBO, like other n,π* excited states, is expected to display electrophilic character.[14,44−46] On the other hand, experimental rate data do not support this conclusion. The fluorescence quenching by the electrophilic O−H hydrogens of aliphatic alcohols, the N−H hydrogens of primary and secondary amines, or the C−H hydrogens of chloroform is in fact very efficient.[21,31,34,36,47] The latter show even larger deuterium kinetic isotope effects than those observed for α C−H hydrogens of aliphatic alcohols or alkanes.[31,34−36] Strikingly, DBO abstracts even hydrogen atoms from water and acetonitrile, which are otherwise considered as photochemically inert.[21,36,47] This has given rise to the hypothesis that singlet-excited DBO may in fact behave as a nucleophilic reactive intermediate.[36]

Hammett-type treatments of rate data within a series of aryl-substituted hydrogen donors appeared essential to unambiguously verify this hypothesis, and the present investigation served precisely this purpose. Indeed, the reaction constant was found to be positive ($\rho = +0.35$ in acetonitrile, cf. Results and Figure 2), giving rise to the very unusual observation (in the field of photochemistry of n,π* excited states) that singlet-excited DBO is quenched more rapidly by more electron-deficient substrates! Namely, electron-donating substituents [*p*-OCH_3 and *m*,*p*-$(CH_3)_2$] resulted in a slower reaction, while electron-withdrawing substitution [*p*-CN and *m*,*m*-$(CF_3)_2$] gave higher rate constants (Table 1). This reactivity pattern is in striking contrast to that expected for hydrogen abstractions by an electrophilic species, for example, the scavenging of *tert*-butoxyl radicals, which gave rise to the conventional reactivity trend (see above).

To the best of our knowledge, this is the first example of an *inverted* electronic substituent effect in a series of chain-breaking antioxidants toward different reactive intermediates, namely, singlet-excited DBO versus *tert*-butoxyl radicals. The positive reaction constant for singlet-excited DBO, which characterizes its inverted reactivity, furnishes the long sought evidence for its nucleophilic reactivity in hydrogen-abstraction reactions.[48] Indeed, the nucleophilicity of singlet-excited DBO is similar, albeit less pronounced, to that well-accepted for carbon-centered radicals.[41,49−51] For example, hydrogen abstraction of *iso*-propyl and *tert*-butyl radicals from a series of toluenes at 303 K (used as neat solvents) yielded reaction constants of +0.80 and +1.00, respectively.[51]

Hydrogen abstraction from benzofuranones yields carbon-centered benzylic radicals.[4,5] Substituent effects could principally originate from a differential stabilization of these primary intermediates, which has been assessed, for example, by the measurement of the respective benzylic C−H BDE. However, any radical-stabilizing aryl substituent effects that could affect the BDE and, therefore, the reaction thermodynamics, are expected to be minor for benzyl-type radicals.[52] The BDEs vary by only 6 kJ mol^{-1} upon changing from electron-accepting (e.g., *p*-CN, *p*-CF_3) to electron-donating (e.g., *p*-OCH_3) substituents in toluene. More importantly, meta-electron-withdrawing substituents are well-known to increase the C−H BDEs of benzylic hydrogens, while both electron-donating as well as electron-withdrawing resonance-active substituents are known to decrease them.[53] These expectations, based on well-established radical-

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[37] The (ground-state) reaction of *tert*-butoxyl radicals with hydrogen donors gives quantitative yields of intermediary radicals and homo- and heterocoupling products derived therefrom (cf. ref 6). In contrast, the photoreaction of singlet-excited DBO with hydrogen donors produces only traces of radicals and derived products (cf. refs 19, 32, 34, and 61) as a result of the interference of a conical intersection on the excited-state hypersurface and efficient back hydrogen transfer in the incipient radical pair (cf. refs 19−21, 31−33, 35, and 47). In line with this expectation, laser-flash photolysis experiments with DBO (OD ca. 0.7, $\lambda_{exc} = 355$ nm) and benzofuranone **12** (85 mM) in acetonitrile yielded only a very weak transient absorption ($\lambda_{obs} = 340$ nm) attributable to traces of the corresponding benzofuranone-derived radical (ca. 5%, quantified relative to the transient radical absorption produced from an optically matched acetonitrile solution of di-*tert*-butylperoxide and **12** upon excitation at 355 nm). Owing to the very low quantum yields for the formation of intermediates and photoproducts, laser-flash photolysis studies and photoproduct studies in dependence on the aryl substituent were not performed for DBO.

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stabilizing effects of aryl substituents, are in sharp qualitative disagreement with the reaction rate data in Table 1 and, therefore, cannot provide a viable explanation. In other words, the reactivity of singlet-excited DBO with aryl-substituted benzofuranones provides no signature of radical-stabilizing effects or the related reaction thermodynamics. In fact, no meaningful correlations with established radical substituent parameters for benzylic radical stabilization[53] were obtained for the quenching of DBO by benzofuranones; for instance, a correlation using Creary's $\sigma_c^{\bullet}$ scale[54] yielded a very poor regression coefficient ($r = 0.198$, $n = 13$). This argument confirms the notion that the positive reaction constant of singlet-excited DBO is truly a consequence of the nucleophilicity of this reactive species and not an indirect consequence of the reaction thermodynamics.

Implications for the Optimization of Antioxidants. The contrasting reactivity of the two reactive species (singlet-excited DBO and *tert*-butoxyl radicals) toward aryl-substituted benzofuranones bears important practical implications for the optimization of these chain-breaking antioxidants. In particular, the relative reactivity of the benzylic C−H hydrogens in these antioxidants depends strongly on the philicity of the abstracting species. Electrophilic radicals (alkoxyl radicals) are more readily scavenged by electron-rich benzofuranones such as methoxy-substituted ones, while nucleophilic radicals (alkyl radicals) are presumably more efficiently intercepted by electron-deficient lactones such as cyano- or trifluoromethyl-substituted derivatives.

This scenario is quite different from the situation found for phenolic antioxidants with reactive O−H hydrogens, where the thermochemistry of the reaction almost always dominates the absolute reactivity and easily overwhelms counteracting polar effects, that is, modulations due to the philicity of the abstracting species. This is due to the fact that substituents, including aryl substituents, have a dramatic effect on the O−H BDEs; for example, they vary by 40 kJ mol^{-1} between *p*-methoxy- and *p*-cyanophenol.[55−57] Hammett reaction constants of reactive species with phenols, for example, are invariably negative [−0.40 for singlet-excited DBO,[20] −0.65 for triplet benzophenone,[9] −0.90 for *tert*-butoxyl radicals,[8] −1.15 for biacetyl,[58] and about −1.6 for the neophyl (2-phenyl-2-methyl-propyl) radical],[59] regardless of whether the abstracting species is inherently electrophilic (triplet ketones and alkoxyl radicals) or nucleophilic (excited azoalkanes or alkyl radicals). The design criteria for the optimization of hydrogen-donor propensity of phenolic antioxidants are, therefore, not transferable to lactone-based antioxidants.

TABLE 2. AM1-Calculated Relative Energies[a] of the Enols Corresponding to 3-Aryl-3*H*-benzofuran-2-ones

	R	ΔE (kJ mol^{-1})		R	ΔE (kJ mol^{-1})
1	*m,m*-(CF$_3$)$_2$	40.6	**9**	H	46.9
2	*p*-CN	73.3	**10**	*m*-CH$_3$	47.7
3	*m*-CN	44.4	**11**	*p*-CH$_3$	47.3
4	*p*-CF$_3$	41.9	**12**	*m,p*-(CH$_3$)$_2$	47.7
5	*p*-COOCH$_3$	72.4	**13**	*p*-OCH$_3$	47.7
6	*m*-CF$_3$	44.0	**14**	*o*-CH$_3$	49.4
7	*p*-Cl	45.2	**15**	*o*-CF$_3$	57.3
8	*p*-F	45.6	**16**	*o,m*-(CH$_3$)$_2$	48.2

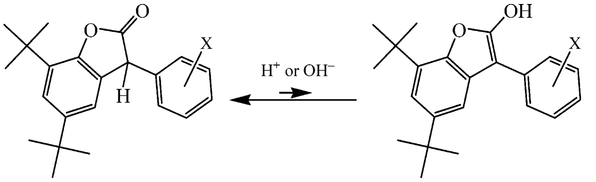
[a] Calculated as *E* (enol) − *E* (lactone).

TABLE 3. AM1-Calculated Relative Energies[a] of the Enols Corresponding to Selected Carbonyl Compounds with Known Enol Contents

	ΔE (kJ mol^{-1})	enol content (%)
ethyl acetate	95.9	no enol found[b]
cyclopentanone	54.0	1.1×10^{-6}[c]
acetophenone	43.5	1.3×10^{-6}[d]
cyclohexanone	30.9	4.2×10^{-5}[c]
benzoylacetone	−2.1	89.2[b]
acetylacetone	−5.4	76.4[b]

[a] Calculated as *E* (enol) − *E* (lactone). [b] From ref 64 for neat ketone. [c] From ref 65 in water. [d] From ref 66 in water.

Involvement of the Enol. The kinetic data for the reaction of singlet-excited DBO as well as *tert*-butoxyl radicals with the investigated benzofuranones are consistent with hydrogen abstraction from the benzylic C−H of the lactone form. For example, the reaction rates for the benzofuranones are 10−100 times larger than those previously determined for the less reactive alkylbenzenes and similar to those determined for diphenylmethanol, which resembles the aryl-substituted benzofuranones with respect to the bisbenzylic structural motif (cf. Results). Interestingly, it was recently suggested, on the basis of the empirical interpretation of solvent effects for phenolic antioxidants,[12,13] that radical scavenging by these lactones may not be attributable to a direct hydrogen abstraction from the benzylic C−H bond but rather from the O−H of the corresponding enol.[30] The latter is necessarily in equilibrium, albeit in small amounts, with the lactone (eq 1).



(1)

To address this mechanistic possibility, we calculated the relative stabilities of the enols corresponding to the benzofuranones **1**−**16** by the semiempirical AM1 method[60] (Table 2). However, no correlation of the calculated relative enol energies with the experimental rate constants for the reaction of either reactive species was observed, as would be expected if the enol was the reactive component. To allow a semiquantitative comparison, we also calculated the relative enol energies by the same method for carbonyl compounds with known enol content (Table 3). Although the calculated (gas-phase) energies are not directly comparable to the experimental data, the trend is extremely gratifying, which reveals that this method can be used as a tool to predict the order of magnitude of the enol content. The relative enol energies for the benzofuranones in Table 2 (ca. 50 kJ mol^{-1}) do, therefore, suggest rather unfavorable enolization equilibria, similar to those of simple ketones. This implies that the enol content in benzofuranones is more likely in the range of 1 ppm or less, too low to contribute significantly to the experimentally observed rate constants of

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singlet-excited DBO and *tert*-butoxyl radicals. Consequently, a competitive reaction with the enol form of the lactones is insufficient to account for the presently established aryl substituent effects. The solvent effects in the hydrogen abstraction from benzofuranones, previously observed for *tert*-butoxyl radicals[7] and presently for singlet-excited DBO (cf. Results), namely, an acceleration in nonpolar solvents, provide presumably no compulsory evidence for the involvement of the enol as an active hydrogen donor. In fact, solvent effects similar to those observed for the benzofuranones are well-known for reactions not involving enols[35,61,62] and can be accounted for by alternative arguments as well, for example, a reduced dipole moment in the transition state. In addition, it is generally accepted that polar hydrogen-bond-accepting solvents strongly stabilize the enol form,[63] which would effectively counterbalance a presumed decrease in enol reactivity in these solvents.

Conclusions

The factors governing the kinetics of hydrogen abstractions are of fundamental importance in mechanistic radical chemistry and antioxidant research. The present study on the hydrogen-donor propensities of aryl-substituted benzofuranones provides an interesting example of a reaction in which the philicity of the abstraction species becomes important and can even lead to an inversion of long-accepted reactivity trends. The *tert*-butoxyl radical showed the expected electrophilic reactivity (faster reaction with electron-rich benzofuranones), while singlet-excited DBO reacted fastest with electron-deficient benzofuranones; the latter result provides a clear-cut manifestation of the nucleophilic character of this reactive species. The sensitive response of benzofuranones (as prototypes of antioxidants with a reactive benzylic C−H group) to the philicity of the abstracting species is in striking contrast to the behavior of phenolic antioxidants for which thermodynamic effects prevail.

Experimental Section

Materials. 2,3-Diazabicyclo[2.2.2]oct-2-ene (DBO) was synthesized as reported.[67] The 3-aryl-3*H*-benzofuran-2-ones were custom synthesized by Ciba Specialty Chemicals, Basel, Switzerland.[68−70] Di-*tert*-butylperoxide (>98%) was used as received. Acetonitrile and *n*-hexane were of UV-spectroscopic quality. Deuteriumoxide had an isotopic purity of >99 atom % D. All experiments were performed at ambient temperature (295 K).

Fluorescence Quenching. Samples were prepared by dissolving DBO (ca. 0.1 mM) in acetonitrile and administering the appropriate amounts of quencher stock solutions with a GC syringe. The samples were degassed by three freeze−pump−thaw cycles to remove oxygen. Homemade quartz cells (4 × 1 × 1 cm) with high-vacuum Teflon stopcocks were used for degassing. The fluorescence lifetime of DBO at ambient temperature (295 K) was measured by a commercial laser-flash photolysis setup incorporating a Nd:YAG laser ($\lambda_{exc} = 355$ nm; full width at half-maximum (fwhm), ca. 4 ns; pulse energy, 7 mJ; $\lambda_{obs} = 430$ nm). The traces were recorded with a digital oscilloscope; 10 traces were accumulated to improve the signal-to-noise ratio and were analyzed by means of least-squares fitting with monoexponential decay functions.

Laser-Flash Photolysis. For the generation of *tert*-butoxyl radicals, acetonitrile solutions containing 25% (v/v) di-*tert*-butylperoxide were irradiated with a 308-nm laser pulse (GSI Lumonics Pulsemaster 846 excimer laser operating with a XeCl fill; fwhm, ca. 10 ns; pulse energy, 80 mJ). The measurements were done with air-equilibrated solutions. The kinetic traces were averaged from two laser pulses, which on the particular setup (1-cm optical path length, side-on irradiation) was sufficient to obtain well-resolved kinetic decay traces. The rise kinetics of the lactone-derived radicals was followed at 340 nm, recorded with a transient digitizer, and analyzed by means of nonlinear least-squares fitting of a combination of a monoexponential rise with a slower monoexponential decay function. These correspond to the kinetics of hydrogen abstraction and the decay of the resulting radicals, respectively.

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