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Benzo[*d*]-1,2-oxaphospholes as Precursors of Stabilized C-Centered Radicals

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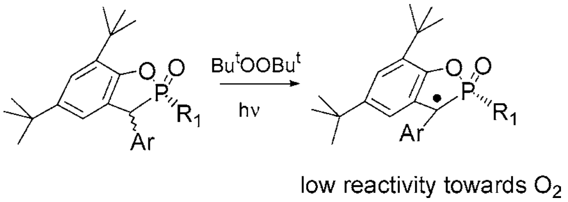
ABSTRACT



Several benzo[*d*]-1,2-oxaphosphole 2-oxides were examined as potential precursors of stabilized C-centered radicals. The transient absorption spectra obtained after laser flash photolysis in the presence of di-*tert*-butyl peroxide showed the features of benzylic radicals with formation and decay kinetics not significantly influenced by the presence of oxygen. In the case of compounds with two possible diastereomeric forms, the C–H bond of the *cis*-isomers is more reactive toward hydrogen abstraction.

Antioxidants are compounds which protect organic materials (polymers, oils) and living organisms against oxidative degradation.[1] In the case of chain-breaking antioxidants, their mechanism of action is based on interference with one of the propagation steps. In this case, they must meet two requirements: (1) they should be good hydrogen donors, and (2) the resulting radicals should exhibit low reactivity toward oxygen. By contrast with heteroatom-centered radicals, most carbon-centered radicals are too reactive toward oxygen.[2,3] This is not usually the case for good hydrogen donors possessing reactive C−H bonds. Interestingly, carbon-centered radicals derived from lactones such as 2-coumaranone react only sluggishly with oxygen.[4] In particular, 5,7-di-*tert*-butyl-3-(3,4-di-methylphenyl)benzo[*b*]furan-23-one (HP-136, for structure see Figure 1B) has been patented[5] and

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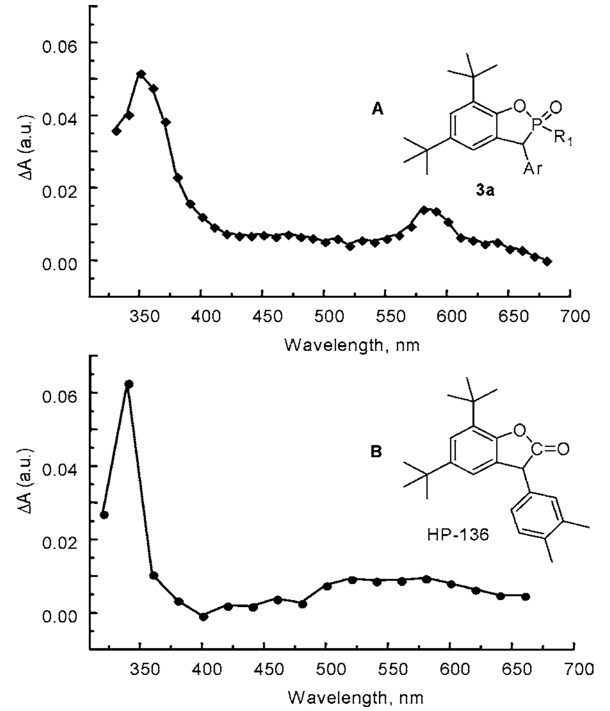


Figure 1. Transient absorption spectra following laser excitation (355 nm) of a sample containing **3a** (2.5 mM) or HP-136 (7.5 mM) in di-*tert*-butyl peroxide/acetonitrile (50/50), under nitrogen, 6 μs after the laser pulse.

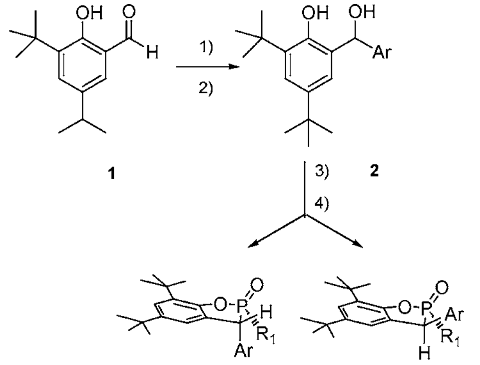
commercialized by CIBA as an antioxidant preventing oxidative degradation of a variety of materials. Also, it has been reported that substitution of carbon-centered radicals by the cyano group has a marked stabilizing effect.[6] In general, the stability of all the above radicals has been explained on the basis of spin density on heteroatom- and/or electron-withdrawing effects adding to stabilization by benzylic delocalization.

On the other hand, the formation of C-centered radicals attached to a phosphorus atom has been previously described.[7] The evidence is strongly against any significant C−P dπ−pπ bonding in the ground state of these radicals and agrees with spin-density essentially localized on the carbon atom. Furthermore, phosphonoyloxyl radicals are similar to carbonyloxyl radicals and have broad and unstructured absorption spectra in the visible region.[8] ESR experiments and theoretical studies have shown that the unpaired electron resides mainly in an orbital composed largely of nonbonding oxygen p-type orbitals, oriented more or less in the O═X−O (X = P or C) plane. The X atom provides only negligible contribution to the SOMO.[8b,9] For instance, in the case of benzoyloxy radicals theoretical calculations predict spin densities of 0.54 on each oxygen and −0.10 on the carbonyl carbon.[9a]

With this as background, it appeared of interest to study the suitability of benzo[*d*]-1,2-oxaphosphole 2-oxides (**3**) (which could be considered as the phosphorus analogues of HP-136) as good hydrogen donors, leading to C-centered stabilized radicals. It has been reported that C$_\alpha$-unsubstituted derivatives of **3** behave as heat stabilizers and antioxidants for organic materials.[10]

Several routes are available for the preparation of benzo[*d*]-1,2-oxaphosphole 2-oxides bearing an ample pattern of substituents on the carbon adjacent to phosphorus.[11] However, the phosphorus analogues of lactone HP-136 have not been previously described. The target compounds were synthesized in a two steps sequence involving the addition of an aryl organometallic reagent to the commercially available aldehyde **1** and subsequent treatment of the resulting hydroxyalkylphenols **2** with PBr$_3$/HBr and then with R$_1$P(OEt)$_2$ (R$_1$= OEt, Ph). Oxaphospholes **3** were obtained as mixtures of diastereomers (Scheme 1, Table 1). The pure compounds were isolated through a combination of precipitation from hexane and column chromatography. In one case, partial hydrolysis of the phosphonate group leading to **3a** was achieved simply by quenching the reaction with ice−water. Under these conditions, the heterocyclic system was

Scheme 1[a]



R$_1$= OH, Ar= 4-MeO-C$_6$H$_4$	**3a**	
R$_1$= OC$_2$H$_5$, Ar= 4-MeO-C$_6$H$_4$	***cis*-3b**	***trans*-3b**
R$_1$= C$_6$H$_5$, Ar= 4-MeO-C$_6$H$_4$	***cis*-3c**	***trans*-3c**
R$_1$= OC$_2$H$_5$, Ar= 3,5-diMe-C$_6$H$_3$	***cis*-3d**	***trans*-3d**

[a] Key: (1) ArLi (2.2 equiv), Et$_2$O, −40 to +25 °C, 2 h; (2) H$_3$O$^+$, then chromatography; (3) R$_1$P(OEt)$_2$ (2 equiv for R$_1$ = Ph; 3 equiv for R$_1$ = OEt), PBr$_3$ (0.4 equiv), 47% HBr (1 drop), toluene, −30 to +25 °C, 6−12 h; (4) 1N NaOH.

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Table 1. δ (^{31}P) (in ppm) and Yield (%) of Compounds **3**

compd[a]	R_1	Ar	δ (^{31}P)	yield[b] (%)
3a	OH	4-MeO-C_6H_4	47.33	59
trans-**3b**	OEt	4-MeO-C_6H_4	43.8	24
cis-**3b**	OEt	4-MeO-C_6H_4	42.77	37
trans-**3c**	Ph	4-MeO-C_6H_4	53.62	48
cis-**3c**	Ph	4-MeO-C_6H_4	61.65	37
trans-**3d**	OEt	3,5-diMe-C_6H_4	44.88	29
cis-**3d**	OEt	3,5-diMe-C_6H_4	43.91	40

[a] The *cis/trans* descriptors indicate the relative arrangement of the substituents R_1 and Ar. [b] Isolated.

not affected.[12] The structural assignment of **3** was straightforward. The presence of the oxaphosphole moiety was revealed by the large ^{31}P,^{13}C coupling constants observed in the ^{13}C NMR spectra for the methine carbon attached to phosphorus ($^1J_{PC}$ ranging from 78.1 to 123.2 Hz) and the C_{ipso} carbon adjacent to the oxygen atom and linked to the ^{t}Bu group ($^3J_{PC}$ ranging from 6 to 9.6 Hz). The relative configuration of the stereoisomers was readily deduced from the NOEs observed in the 2D gNOESY spectra. Thus, the *ortho* protons of the *P*-phenyl ring of ***trans*-3c** and ***cis*-3c** correlate, respectively, with the methine proton at δ 4.53 ppm (dt, $^2J_{PH}$ 8.1, $^4J_{HH} = {}^6J_{HH}$ 0.9 Hz) and the *ortho* protons of the *p*-methoxy substituent at δ 6.78 ppm (dd, $^3J_{HH} = 7.8$ Hz).

Laser flash photolysis ($\lambda = 355$ nm) of di-*tert*-butyl peroxide in deaerated acetonitrile (50% v/v) in the presence of **3a** (2.5 mM) were carried out in order to generate the corresponding benzylic radical and to study its reactivity with oxygen.[13] The resulting transient species showed one strong UV band with maximum at 350 nm and a less intense broad band with maximum in the visible at 580 nm (Figure 1A). For comparison, the transient absorption spectrum obtained upon photolysis of di-*tert*-butyl peroxide in the presence of HP-136 in the same solvent is shown in Figure 1B.[14] In the presence of oxygen, the rates of growth and decay of the oxaphosphole oxide radical (**4a**) were essentially the same as under nitrogen, indicating a low reactivity toward oxygen (Figure 2). These data suggest that the phosphonyl group in radical **4a** provides a stability to the benzylic radical similar to that of the carbonyl group in HP-136.

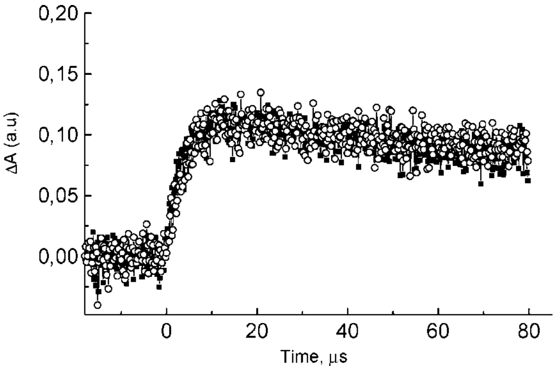

Figure 2. Transient kinetic traces recorded at 340 nm following 355 nm laser excitation of a sample containing 2.5 mM of **3a** in di-*tert*-butylperoxide/acetonitrile (50/50) under nitrogen (■) and oxygen (○).

The growth of the radical signal reflects the hydrogen abstraction process (k_2) and other forms of decay of *tert*-butoxyl radicals (k_0), such as reaction with the solvent and β-cleavage. The experimental rate constant for the growth is given by eq 3 in Scheme 2.

Scheme 2. H-Abstraction Process by *tert*-Butoxyl Radicals

$$ {}^tBuOO{}^tBu \xrightarrow{h\nu} 2\ {}^tBuO^\bullet \qquad (1)$$

$$ {}^tBuO^\bullet + R\text{-}H \longrightarrow {}^tBuOH + R^\bullet \qquad (2)$$

$$ k_{expt} = k_0 + k_2\,[R\text{-}H] \qquad (3)$$

Accurate measurements of the rate constant for the hydrogen abstraction process could not be done due to the poor solubility of the phospholane oxides, which prevented to obtain kinetic data at different concentrations. Then, the efficiency of benzylic radical formation from **3a** was estimated by comparison with HP-136, using the same concentration for both compounds. Figure 3 shows the transient kinetic traces at the corresponding UV maxima obtained upon laser excitation of the peroxide in the presence of 2.5 mM solutions of **3a** or HP-136.

The same types of studies were carried out with both diastereomers of compounds **3b**−**d**. For all of them, the generated radicals exhibited similar transient absorption spectrum as that obtained from **3a**; oxygen did not produce any appreciable change in the growth or decay rate of these radicals. However, comparison of the transient kinetic traces recorded at 360 nm for each diastereomeric pair at the same concentration revealed important differences in the relative absorbances (see Figure 4 for ***cis*-3b** and ***trans*-3b** as an example). It should be taken into account that, as mentioned above, the growth of the signal reflects not only the hydrogen atom abstraction by *tert*-butoxyl radical from the benzylic position, but also other forms of decay of this radical. Hence, this fact evidences a marked dependence of the hydrogen

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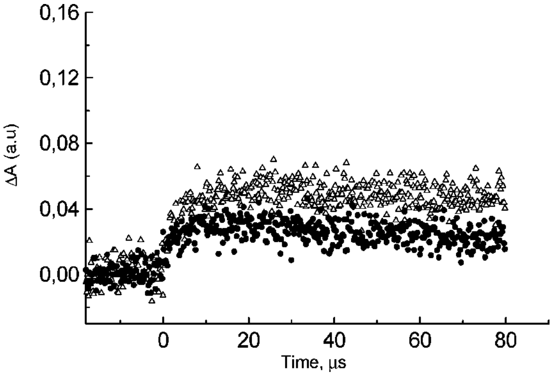

Figure 3. Transient kinetic traces recorded at the corresponding maxima following 355 nm laser excitation of a sample containing 2.5 mM of **3a** (△, at 355 nm) and HP-136 (●, at 340 nm) in di-*tert*-butylperoxide/ acetonitrile (50/50) under nitrogen.

abstraction rate on the substrate configuration. In all cases, the *cis*-stereoisomer showed the higher efficiency for benzylic radical formation (between 4 and 10 times higher than that of the *trans*-stereoisomer). A possible explanation could be a favored hydrogen abstraction from the *cis*-stereoisomer due to stabilization of the transition state by interaction between the developing radical center and the P═O bond. Studies are in progress in order to gain further insight into this effect.

In summary, comparison of the behavior of HP-136 and **3a** toward *tert*-butoxyl radicals and the reactivity of the generated benzylic radicals has demonstrated the suitability of **3a** as precursor of stabilized C-centered radicals, a property associated with antioxidant potential. Using both diasteromers of benzo[*d*]-1,2-oxaphosphole 2-oxides a dramatic stereodifferentiation in the hydrogen abstraction efficiency has been revealed.

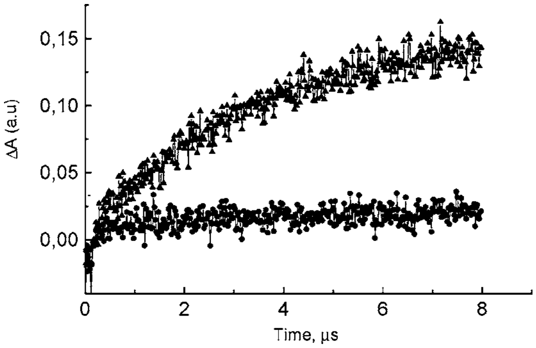

Figure 4. Transient kinetic traces recorded at 360 nm following 355 nm laser excitation of a sample containing 7.2 mM of ***cis*-3b** (▲) and ***trans*-3b** (◆) in di-*tert*-butylperoxide/acetonitrile (50/50) under nitrogen.

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Supporting Information Available: Synthetic procedures and characterization for the preparation of heterocycles **3**, transient absorption spectra (for ***cis*-3b**, ***trans*-3b**, and ***cis*-3d**), and transient kinetic traces (for ***cis*-3c**, ***trans*-3c**). This material is available free of charge via the Internet at http://pubs.acs.org.

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