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Influence of Substitution at the Benzylic Position on the Behavior of Stereoisomeric Phosphorus Compounds as Precursors of Stabilized Carbon-Centered Radicals

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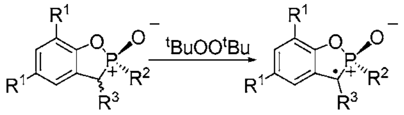
ABSTRACT



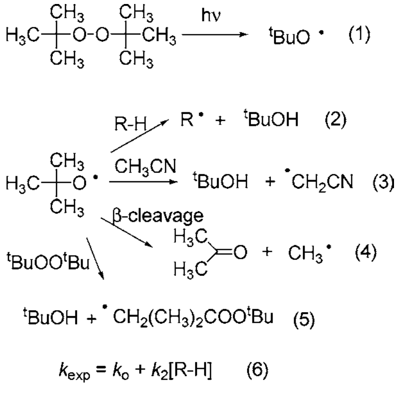
diastereodifferentiation factor:
R^3 = alkyl: *cis/trans* up to 9.50
R^3 = aryl: *trans/cis* up to 7.26

Efficient benzylic radical formation from benzo[*d*]-1,2-oxaphospholes has demonstrated their suitability as precursors of stabilized C-centered radicals, a property associated with antioxidant potential. A remarkable stereodifferentiation is observed for alkyl- and aryl-substituted derivatives.

Antioxidants capable of blocking free-radical chain processes must meet two requirements: (1) they should be good hydrogen donors and (2) the resulting radicals should exhibit low reactivity toward oxygen.[1]

One of the strategies to determine the ability of a molecule to act as antioxidant is the use of transient absorption spectroscopy to investigate the reactivity of *tert*-butoxy radicals toward H-donors (Scheme 1). Thus, upon laser excitation of di-*tert*-butyl peroxide, the O−O bond dissociates, affording two *tert*-butoxy radicals. These species decay by reaction with the solvent (acetonitrile in Scheme 1), β-cleavage, and reaction with peroxide.[2] The above processes can compete with hydrogen abstraction when the irradiation is performed in the presence of a good hydrogen donor (R−H in Scheme 1). If the new radicals have suitable absorption bands, their formation and reactivity can be studied by the laser flash photolysis (LFP) technique.

Scheme 1. Generation of *tert*-Butoxyl Radicals and Subsequent Reactions



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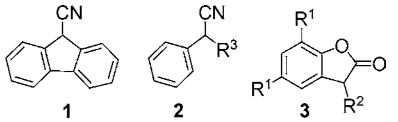


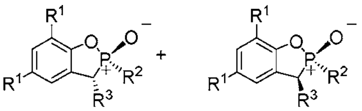
1 **2** **3**

R^1 = H, ^{t}Bu
R^2 = H, CH_3, Ar
R^3 = H, Ar

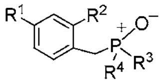
Figure 1. Compounds leading to stabilized C-centered radicals.

In particular, hydrogen abstraction from benzylic positions by *tert*-butoxy radicals occurs with convenient rate constants (toluene: $k_2 = 0.23 \times 10^6$ M^{-1} s^{-1}, 2-phenylethane: $k_2 = 1.05 \times 10^6$ M^{-1} s^{-1}, diphenylmethane: $k_2 = 0.91 \times 10^6$ M^{-1} s^{-1});[2,3] the resulting C-centered radicals show an intense absorption band at $\lambda_{max} > 310$ nm.[4] Electron-withdrawing substituents at the benzylic position, as in aryl acetates, usually slow the hydrogen abstraction rate due to the electrophilicity of the *tert*-butoxy radical;[5] this does not happen with arylacetonitriles (**1** and **2**) or lactones **3** (Figure 1).[6,7] In addition, though benzylic radicals usually show high reactivity toward oxygen,[8] limiting the potential use of their precursors as antioxidants, those derived from compounds **1**−**3** remain practically unreactive in the time-scale of LFP measurements.[6,7] The unique behavior of these systems has been attributed to the combined effect of some of the following parameters: (1) benzylic resonance stabilization, (2) spin delocalization into the carbonyl or cyano heteroatom, (3) electron-withdrawing effects, (4) steric effects, and in the case of compounds **3**, also (5) the forced planarity introduced by the five-membered rings.

We have previously reported that benzo[*d*]oxaphospholes **4**−**6** can be useful as precursors of stabilized carbon-centered radicals (Figure 2).[9] Interestingly, the presence of phosphorus in their structure gives rise to the formation of two diastereoisomers. In the case of **5** and **6**, this structural feature has allowed the study of diastereodifferentiation in hydrogen abstraction by *tert*-butoxy radicals. It has been found that the compounds with the aryl substituents *trans* to the ethoxy group are much more reactive than their *cis* stereoisomers.



R^1 = ^{t}Bu, R^2 = OH, R^3= p-$OCH_3C_6H_4$	**4**	
R^1 = ^{t}Bu, R^2= OC_2H_5, R^3 = *p*-$OCH_3C_6H_4$	***(R*** (R_P,R)**-5**	(R_P,S)**-5**
R^1 = ^{t}Bu, R^2= OC_2H_5, R^3 = 3,5-$(CH_3)_2C_6H_3$	(R_P,R)**-6**	(R_P,S)**-6**
R^1 = H, R^2= OC_2H_5, R^3 = H	**7**	
R^1 = ^{t}Bu, R^2= OC_2H_5, R^3 = H	**8**	
R^1 = ^{t}Bu, R^2= OC_2H_5, R^3 = CH_3	(R_P,R)**-9**	(R_P,S)**-9**
R^1 = ^{t}Bu, R^2= OC_2H_5, R^3 = CH_3CH_2	(R_P,R)**-10**	(R_P,S)**-10**
R^1 = ^{t}Bu, R^2= OC_2H_5, R^3 = $(CH_3)_2CH$	(R_P,R)**-11**	(R_P,S)**-11**



R^1 = R^2 = H, R^3= R^4= C_6H_5	**12a**
R^1 = R^2 = H, R^3= C_6H_5, R^4= OC_2H_5	**12b**
R^1 = R^2 = H, R^3= R^4= OC_2H_5	**12c**
R^1 = CH_3, R^2 = H, R^3= R^4= OC_2H_5	**12d**
R^1 = OCH_3, R^2 = H, R^3= R^4= OC_2H_5	**12e**
R^1 = NH-BOC, R^2 = H, R^3= R^4= OC_2H_5	**12f**
R^1 = H, R^2 = OCH_3, R^3= R^4= OC_2H_5	**12g**
R^1 = H, R^2 = OH, R^3= R^4= OC_2H_5	**12h**

Figure 2. Phosphorus compounds.

We wish now to report on the results obtained with 3-alkyl-substituted derivatives **9**−**11**, whose study was undertaken in order to understand the factors involved in the intriguing diastereodifferentiation observed with **5** and **6**. In addition, compounds **7** and **8**, lacking the substituent at the benzylic position, as well as the noncyclic analogues **12**, have been also studied to determine whether the phosphorus-containing heterocycle plays a key role. Furthermore, steady-state photolysis studies have been carried out; the main products are diasteroisomers resulting from cross-coupling between the oxaphosphole system and the solvent. These products are formed in a diastereomeric ratio that is independent from the precursor configuration, indicating that the C-centered radical does not show any memory effect.

The required oxaphospholes were synthesized in a two-step sequence involving addition of an organometallic reagent or reduction with $NaBH_4$ of the corresponding commercially available 2-hydroxyaldehyde and subsequent treatment of the resulting hydroxyalkylphenols with triethyl phosphite (for details see the Supporting Information). The structure of the new products was assigned on the basis of the large coupling constant between the phosphorus nucleus and the methine carbon of the five-membered ring (average value of $^1J_{PC} >$ 119 Hz). The relative configuration was determined by means of 1D gNOESY experiments. Selective inversion of the methylene protons of the ethoxy group produced a NOE enhancement on the nearby protons of the benzylic substituent for compounds having a *cis* arrangement of these moieties (Figure S4, Supporting Information).

LFP (Nd:YAG laser, λ_{exc} = 355 nm, 10 ns pulse) of deaerated mixtures of di-*tert*-butyl peroxide and acetonitrile (50% v/v) containing the phosphorus compounds **12a**−**g** did

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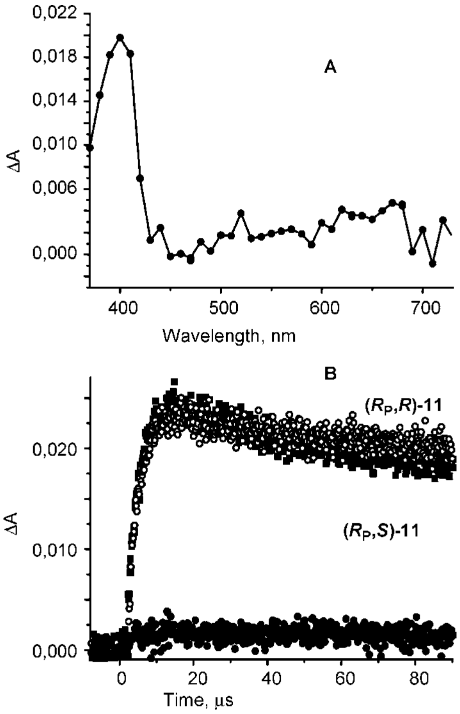

Figure 3. (A) Transient absorption spectrum recorded following laser excitation (355 nm) of a sample containing **(*R*p,*R*-11)** (10 mM) in di-*tert*-butyl peroxide/acetonitrile (50/50 v/v), under nitrogen, 2 μs after the laser pulse. (B) Transient kinetic traces recorded at 400 nm following 355 nm laser excitation of a sample containing 10 mM of either **(*R*p,*R*)-11** [under nitrogen (○) and oxygen (■)] or **(*R*p,*S*)-11** [under nitrogen (●)] in di-*tert*-butyl peroxide/acetonitrile (50/50 v/v).

not produce any detectable transient absorption spectra in the UV−vis range. Compound **12h** led to the typical spectrum of phenoxy radicals (not shown),[10] so no hydrogen abstraction from the benzylic C−H bond was detected. These results clearly demonstrate low reactivity of the noncyclic phosphoric compounds **12**, which must be related with the low nucleophilicity of the benzylic C−H bond. Thus, it seems that planarity is essential for an adequate reactivity.

Benzo[*d*]-1,2-oxaphospholes **7**−**11** were studied under similar conditions, and the results were compared with those obtained with **4**−**6**. The transient absorption spectrum, together with the transient kinetic traces, is shown in Figure 3 for **11**; similar results were obtained for **7**−**10**. In all cases, the rates of growth and decay of the benzylic radicals were essentially the same in the presence of oxygen as under nitrogen, indicating a low reactivity toward oxygen in the LFP time scale ($k_{O2} < 5 \times 10^3$ M^{-1} s^{-1}) [Figure 3B, kinetic traces under nitrogen and air for **(*R*$_P$,*R*)-11**].

As expected from radical stability considerations, alkyl substituents were less efficient than aryl groups in promoting H-atom abstraction from the benzo[*d*]-1,2-oxaphospholes.

Table 1. Comparison between the Relative Efficiencies (vs HP-136) of Phosphorus Heterocycles **4**−**11** as Hydrogen Donors, Together with the Diastereodifferentiation Factors (Where Applicable)

compd	relative efficiency (vs HP-136)	compd	relative efficiency (vs HP-136)[a]	diastereo-differentiation factor
4	2.19			
(R_P,R)-**5**	0.19	(R_P,S)-**5**	1.38	0.14
(R_P,R)-**6**	0.42	(R_P,S)-**6**	1.48	0.28
7	0.23			
(R_P,R)-**9**	0.47	(R_P,S)-**9**	0.31	1.52
(R_P,R)-**10**	0.27	(R_P,S)-**10**	0.09	3.00
(R_P,R)-**11**	0.38	(R_P,S)-**11**	0.04	9.50

[a] HP-136: 5,7-di-*tert*-butyl-3-(3,4-dimethylphenyl)benzo[*b*]furan-2-one.

However, this was only true for the *trans* stereoisomers. Besides, a remarkable influence of substitution at the benzylic position on the behavior of the stereoisomeric phosphorus compounds was observed: while in aryl-substituted derivatives the *trans*-stereoisomer showed higher efficiency of radical formation, the *cis*-isomer was more reactive in the alkyl-substituted analogues.

Diastereodifferentiation could be explained by the steric hindrance associated with a *tert*-butoxy radical approach to the hydrogen atom and by the degree of planarity of the benzo[*d*]oxaphosphole system. The first factor would predominate in the alkyl derivatives. Such steric effects would be also present in the aryl-substituted compounds. However, in these cases, the stabilization of the transition state leading to the benzylic radical would be less favorable for the stereoisomer with a *cis* arrangement of the ethoxy and aryl substituents. The degree of planarity required for an efficient electronic delocalization of the developing radical center through the aryl substituent would cause larger steric interactions in the *cis* stereoisomer as compared with the situation in the *trans* derivatives (see the modelization of methyl- and phenyl-substituted benzooxaphosphole diastereomeric pairs in Figure S18, Supporting Information).

Finally, product studies with **(*R*$_P$,*R*)-5** and **(*R*$_P$,*S*)-5** were performed in order to determine the type of products formed in the absence of air. Interestingly, three cross-coupling products arising from reaction between C-centered radicals (a solvent-derived radical and the benzylic radical) were observed, namely the pair of diastereoisomers **13** and the product of partial hydrolysis of the phosphonate moiety (**14**). The same diastereomeric ratio (5:1 as measured by GC/MS) of compounds **13** was obtained independently of the configuration of the oxaphosphole. However, as expected from the relative efficiencies of hydrogen abstraction (Table 1), a higher yield of product formation was obtained in the case of the **(*R*$_P$,*S*)-5** stereoisomer. It is very interesting that no homodimers are formed. A reasonable explanation could be based on the Fischer−Ingold persistent free-radical effect, which in the case of persistent and transient radicals always favors the formation of the cross dimer.[11]

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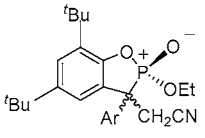

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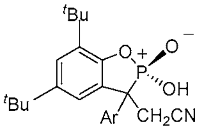

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Ar = p-OMeC$_6$H$_4$

With the acyclic material **12c**, the product arising from reaction between the solvent-derived radical and the benzylic radical was also observed. However, as expected from the low efficiencies of hydrogen abstraction from this substrate, a much lower yield of product formation was obtained than when using **(*R*$_P$,*S*)-5** under the same conditions (9% for the former as compared with 85% for the latter, after 20 h of irradiation, see Figures S16 and S17 in the Supporting Information).

In summary, the behavior of phosphorus compounds with a hydrogen atom at the benzylic position toward *tert*-butoxy radicals has revealed the importance of planarity for H-abstraction to compete with the natural decay of *tert*-butoxy radicals. Comparison of the efficiency in benzylic radical formation between benzo[*d*]-1,2-oxaphospholes and HP-136 has demonstrated the suitability of the former as precursors of stabilized C-centered radicals, a property associated with antioxidant potential. Using both diastereoisomers of 3-substituted benzo[*d*]-1,2-oxaphospholes, a remarkable stereodifferentiation is observed for alkyl and aryl-substituted derivatives. Finally, two cross-coupling compounds, arising from coupling between substrate- and solvent-derived radicals, are obtained. The lack of diastereodifferentiation in their formation reveals that, once formed, the benzylic radicals do not show any memory effect.

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Supporting Information Available: Transient kinetic traces for **7**, **9**, and **10**, as well as experimental procedures and spectroscopic data for all new compounds. Also, a modelization of methyl- and phenyl-substituted benzooxaphosphole diastereomeric pairs is included. This material is available free of charge via the Internet at http://pubs.acs.org.

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