JOC Article

Determination of the Substituent Effect on the O−H Bond Dissociation Enthalpies of Phenolic Antioxidants by the EPR Radical Equilibration Technique

Giovanni Brigati, Marco Lucarini,* Veronica Mugnaini, and Gian Franco Pedulli*

Dipartimento di Chimica Organica "A. Mangini", Università di Bologna, Via S. Donato 15, I-40127 Bologna, Italy

lucarini@alma.unibo.it; pedulli@alma.unibo.it

Received March 25, 2002

The bond dissociation enthalpies (BDE) of several phenols containing electron-withdrawing substituents in the *para* position have been determined by means of the EPR radical equilibration technique. It has been found that CN, NO_2, CHO, COOR, and COOH induce an increase of the BDE value of the O−H bond, thus producing a worsening of the antioxidant activity of phenols, while Cl, Ph, and CH═CHPh show an opposite effect. The contributions of these substituents for the calculation of the BDE values in polysubstituted phenols by using the group additivity rule have also been derived. It is shown that this rule provides quite reliable predictions of bond strengths, so that the method can be conveniently used to estimate new data on substituted phenols.

Introduction

Phenolic compounds are both widespread in nature and largely used in synthetic organic materials because of their protective action against oxidative degradation of the host substrates.[1] The antioxidant properties of phenols are due to their ability to quench the chain carrying peroxyl radicals of the substrate by transfer of the hydroxylic hydrogen to form hydroperoxides.[2] Since the rate constants of this reaction depend largely on the strength of the O−H bond, many studies have been reported in the recent literature on the determinations of the bond dissociation enthalpies (BDEs) of phenolic derivatives, with the aim of understanding how the strength of the phenolic bond is affected by nature, position, and number of substituents.[3] The experimental methods more frequently used to measure BDE values are a photoacoustic technique,[4] a procedure based on the use of thermodynamic cycles by combining the heat of heterolysis of a given species and the redox potentials of the resulting ions,[5] and the determination by EPR spectroscopy of the equilibrium constant between couples of phenols and of the corresponding phenoxyl radicals.[6]

Besides these experimental studies, a number of theoretical investigations of varying degrees of sophistication have also been reported in order to understand the structural factors determining the stability of the O−H phenolic bond.[3,7−10] Both experimental and theoretical results indicate that the change of the O−H bond strength due to a given substituent is approximately constant in the variously substituted phenols and that, for each substituent in the *ortho*, *meta*, and *para* positions, an additive contribution may be derived that can be used to estimate the bond dissociation enthalpies $DH°$(ArO−H) of polysubstituted phenols for which experimental data are lacking.[3,11] It is therefore important to know the experimental parameters for a larger number of substituents as possible.

Although the additive contributions are known for many electron-releasing groups, electron-withdrawing substituents have been seldom investigated[12] because their presence is associated with an enhancement of the O−H BDE value and thus with both a worsening of their antioxidant activity and a reduction of their persistence due to the increased reactivity of the related phenoxyl radicals.

To provide additional data for substituents scarcely investigated so far, we have undertaken an experimental study of phenols containing electron-withdrawing substituents in the *para* position, by measuring the O−H BDE values by using the EPR radical equilibration technique. This, among the various experimental meth-

---

[1] Denisov, E. T.; Khudyakov, I. V. *Chem. Rev.* **1987**, *87*, 1313.

[2] Howard, J. A. In *Free Radicals*; Kochi, J. K., Ed.; John Wiley and Sons: New York, 1973.

[3] Borges dos Santos, R. M.; Martinho Simões, J. A. *J. Phys. Chem. Ref. Data* **1998**, *27*, 707.

[4] Laarhoven, L. J. J.; Mulder, P.; Wayner, D. D. M. *Acc. Chem. Res.* **1999**, *32*, 349 and references therein.

[5] (a) Bordwell, F. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1991**, *113*, 1736. (b) Bordwell, F. G.; Zhang, X.-M. *J. Org. Chem.* **1990**, *55*, 6078. (c) Bordwell, F. G.; Zhang, X.-M. *J. Phys. Org. Chem.* **1995**, *8*, 529.

[6] (a) Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Cabiddu, S.; Fattuoni, C. *J. Org. Chem.* **1996**, *61*, 9259. (b) Lucarini, M.; Pedulli, G. F.; Cipollone, M. *J. Org. Chem.* **1994**, *59*, 5063.

[7] Bordwell, F. G.; Zhang, X. M.; Satish, A. V.; Cheng, J. P. *J. Am. Chem. Soc.* **1994**, *116*, 6605.

[8] Wu, Y. D.; Lai, D. K. W. *J. Org. Chem.* **1996**, *61*, 7904.

[9] Wright, J. S.; Carpenter, D. J.; McKay, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1997**, *119*, 4245.

[10] Brinck, T.; Haeberlein, M.; Jonsson, M. *J. Am. Chem. Soc.* **1997**, *119*, 4239.

[11] Wright, J. S.; Johnson, E. R.; DiLabio, G. A. *J. Am. Chem. Soc.* **2001**, *123*, 1173.

[12] Jackson, S. A.; Hosseini, K. M. *J. Chem. Soc., Chem. Commun.* **1992**, 967.

10.1021/jo025755y CCC: $22.00

TABLE 1. EPR Spectral Parameters of 4-Substituted 2,6-Di-*tert*-butylphenoxyl Radicals and $DH°$(ArO−H) Values (BDE) of the Parent Phenols in Benzene

substituent	$a_{3,5}$ (gauss)	a_{other} (gauss)	*g*-factor	BDE (kcal/mol)
NO_2	2.23	2.23 (1N)	2.0053	84.94
COOH	2.16		2.0047	84.27
COOMe	2.14	0.53 (3H)	2.0050	84.10
CHO	2.10	0.45 (1H)	2.0054	84.23
CN	2.17	1.37 (1N)	2.0048	84.24
H	1.95	9.72 (1H), 0.07 (18H)	2.0047	82.80[6a]
Cl	1.87	1.47 (^{35}Cl), 1.22 (^{37}Cl)	2.0058	82.41
Ph	1.73	1.73 (3H), 0.67 (2H)	2.0044	81.24
Me_3C	1.71	0.38 (9H)	2.0046	81.24[6a]
Me	1.67	11.20 (3H)	2.0046	81.02[6a]
RS	1.39		2.0055	81.03[6b]
PhCH=CH	1.55	6.39 (1H), 2.85 (1H), 1.55 (3H), 0.57 (2H)	2.0040	78.90
MeO	0.93	1.53 (3H)	2.0047	78.31[6a]

ods used for the determination of bond strengths, seems to guarantee at present the best accuracy since even relatively large errors in the measurement of radical concentrations and therefore of the equilibrium constant, K_e, give rise to small errors in the BDE value due to the logarithmic relation connecting these two quantities.

Results and Discussion

All of the investigated compounds are 4-substituted 2,6-di-*tert*-butylphenols. These have been chosen because of the large persistence characterizing phenoxyl radicals where the radical oxygen center is sterically protected. In these radicals the reactions leading to their decay, such as dimerization or disproportionation, are slower than for phenoxyl radicals without *ortho* substituents. The radicals were produced by photolyzing inside the EPR cavity deoxygenated benzene solutions of the phenol (ca. 0.1 M) containing 0.1 M of di-*tert*-butyl peroxide. The EPR spectra of the investigated radicals consisted in all cases of a triplet, due to the coupling with the two *meta* protons, of multiplets arising from the coupling with the nuclei of the *para* substituent. Only when the latter group was a phenyl or a styryl substituent were the EPR spectra of some complexity. The measured spectral parameters are reported in Table 1 together with those of structurally related radicals containing *para* electron-releasing groups.[6a]

The determination of the O−H bond dissociation energies was done by measuring the equilibrium constant, K_1, for the hydrogen atom transfer reaction between two phenols and the corresponding phenoxyl radicals (eq 1) generated under continuous photolysis:[6,13]

$$\mathrm{ArOH} + \mathrm{Ar'O}^{\bullet} \rightleftharpoons \mathrm{ArO}^{\bullet} + \mathrm{Ar'OH} \qquad (1)$$

Experiments were performed on concentrated solutions of the phenols (≥0.1 M) so that, in the calculation of K_1, the initial concentration of ArOH and Ar′OH could be used, while the relative radical concentrations were determined by means of EPR spectroscopy.

The BDEs for the species ArOH were calculated, in the assumption that the entropic term can be neglected,[6] by means of eq 2 from K_1 and the known BDE value of a reference species Ar′OH, i.e., 2,4,6-tri-*tert*-butylphenol, whose O−H BDE value in benzene has been measured by a conventional calorimetric method as 81.24 kcal/mol.[14]

$$\mathrm{BDE(ArO{-}H)} = \mathrm{BDE(Ar'O{-}H)} - RT\ln(K_1) \qquad (2)$$

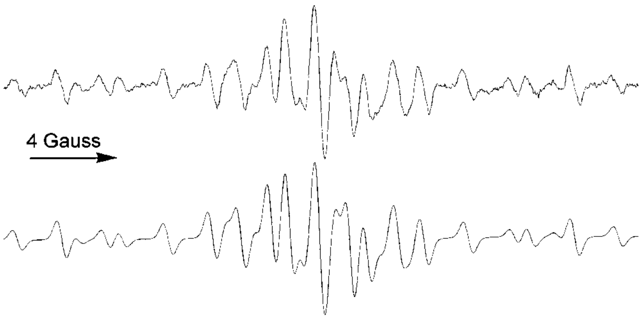


FIGURE 1. Central part of the room-temperature EPR spectrum observed under continuous irradiation of a benzene solution containing di-*tert*-butyl peroxide (10% v/v), 0.28 M 2,6-di-*tert*-butyl-4-cyanophenol, and 0.14 M 2,6-dimethylphenol.

Figure 1 shows, as an example, the central part of the EPR spectrum obtained under irradiation of a benzene solution of 0.28 M 2,6-di-*tert*-butyl-4-cyanophenol, 0.14 M 2,6-dimethylphenol, and 10% (v/v) $(Me_3CO)_2$, together with the corresponding computer simulation. From the experimentally determined radical concentrations, the BDE value of the cyano-substituted phenol is calculated to be 0.26 kcal/mol lower than that of 2,6-dimethylphenol (84.50 kcal/mol),[6] i.e., 84.24 kcal/mol. The equilibration conditions for the reaction of eq 1 were checked by repeating the measurements under different concentrations of the reactants and light intensity.

Similar experiments led to the determination of the BDE values of the other examined phenols, the resulting data being collected in Table 1 and, in a more pictorial form, in Figure 2. It is seen that the data are strongly dependent on the nature of the *para* substituents, higher BDE values being observed with electron acceptors and lower values with electron-releasing substituents, the measured bond strengths spanning a range of ca. 7 kcal/mol.

It should be emphasized that these values are lower than in *para* substituted phenols having free *ortho*

---

(13) Pedulli, G. F.; Lucarini, M.; Pedrielli, P. In *Free Radicals in Chemistry, Biology and Environment*; Minisci, F., Ed.; Kluwer Academic Publishers: 1997; p 169.

(14) Mahoney, L. R.; Ferris, F. C.; DaRooge, M. A. *J. Am. Chem. Soc.* **1969**, *91*, 3883.

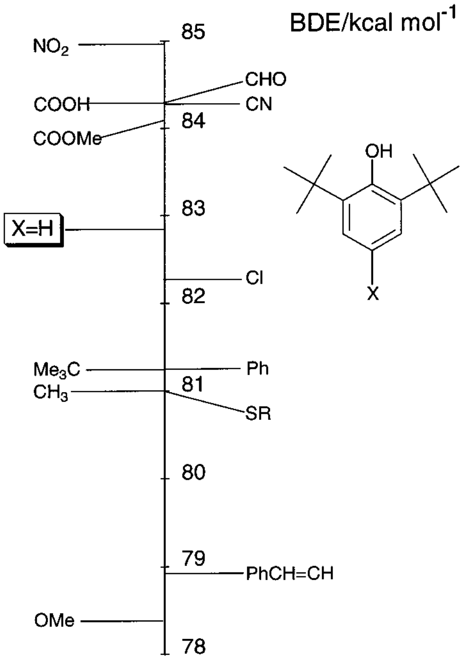
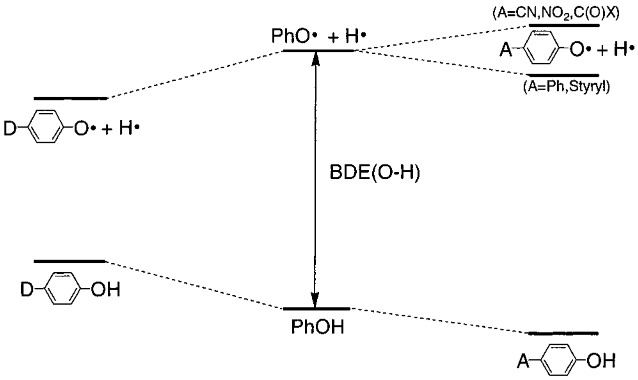


FIGURE 2. Experimental O−H bond dissociation enthalpy values of 4-substituted 2,6-di-*tert*-butylphenols measured in benzene solutions.

SCHEME 1



positions, since the steric repulsion between the hydroxyl and the bulky *tert*-butyl groups destabilizes the starting phenol by forcing the OH group (still coplanar with the aromatic ring) to be bent with respect to its "natural angle",[15] thus producing a decrease of the O−H bond strength. An explanation of the *para* substituent effect has been given in many theoretical papers[7−10] and can be summarized as follows (see Scheme 1). The O−H BDE is given by the difference between the energy of the phenoxyl radical (plus that of the hydrogen atom) and that of the starting phenol, and any substituent destabilizing the phenol (ground-state effect) and/or stabilizing the phenoxyl radical (radical effect) reduces the O−H bond strength. On the other hand, substituents stabilizing the phenol and/or destabilizing the phenoxyl radical have an opposite effect.

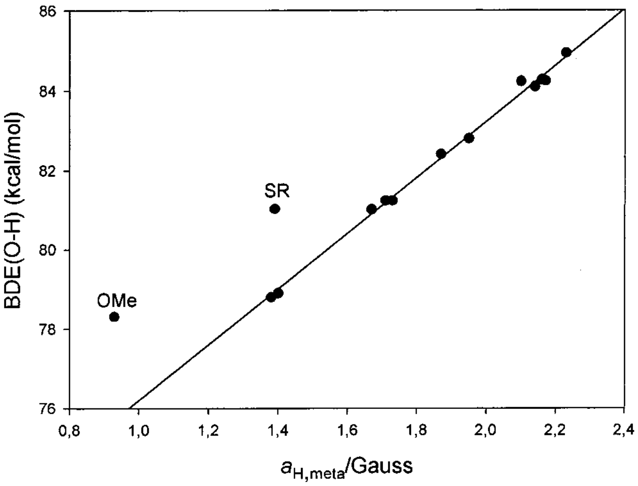


FIGURE 3. Bond dissociation enthalpy values of 4-substituted 2,6-di-*tert*-butylphenols against the room-temperature hyperfine splittings at the *meta* protons measured in benzene solutions of the corresponding phenoxyl radicals.

Because, on passing from phenols to the corresponding phenoxyl radicals, the terminal group changes its electronic properties from releasing (for the hydroxyl group) to strongly accepting (for the radical oxygen atom), when the substituent in position 4 is a donor, the *para* interaction is repulsive in the phenol (destabilizing) and attractive in the phenoxyl radical (stabilizing), the overall effect being a decrease of the O−H BDE. With electron-withdrawing substituents containing heteroatoms such as CN, NO_2, COR, etc., the *para* interaction is stabilizing in the phenol and destabilizing in the phenoxyl radical, this producing an increase of the O−H bond strength. When the substituent is an unsaturated hydrocarbon group (aryl or styryl), the unpaired electron is highly delocalized in the substituent, with a consequent strong stabilization of the phenoxyl radical and decrease of the BDE value for the O−H bond.

To try to estimate the relative importance of the ground-state effect and of the radical effect, the experimental BDE values of 2,6-di-*tert*-butyl-4-substituted phenols were plotted against the *meta* proton hyperfine splitting constants measured in the corresponding phenoxyl radicals (Figure 3). These radicals are known to have an odd alternate spin population pattern with large positive spin densities at the oxygen and at the *ortho* and *para* positions and small negative spin densities at the other ring positions including the *meta* carbons. This is the pattern expected on the basis of the canonical structures **A**−**D** not involving charge separation. Also the higher energy polar structures **E**−**G**, although less important, contribute to the description of the electronic properties of the phenoxyl radical, the expected spin density pattern being, in this case, complementary to that predicted for structures **A**−**D**, i.e., positive for the *meta* and *ipso* positions and negative for the positions *ortho* and *para* to the oxygen radical center. The decrease of the *meta* proton splittings observed by reducing the electron acceptor character of the *para* substituents can be interpreted in terms of an increasing weight of structures **E**−**G** (inducing at the *meta* carbons opposite spin densities with respect to **A**−**D**). At the same time, the larger contribution of these polar structures produces a stabilization of the phenoxyl radical and thus a decrease of the BDE value. Actually, the plot of Figure 3 shows that O−H bond strengths and *meta* proton split-

---

(15) Ingold, K. U. *Can. J. Chem.* **1962**, *40*, 111.

SCHEME 2

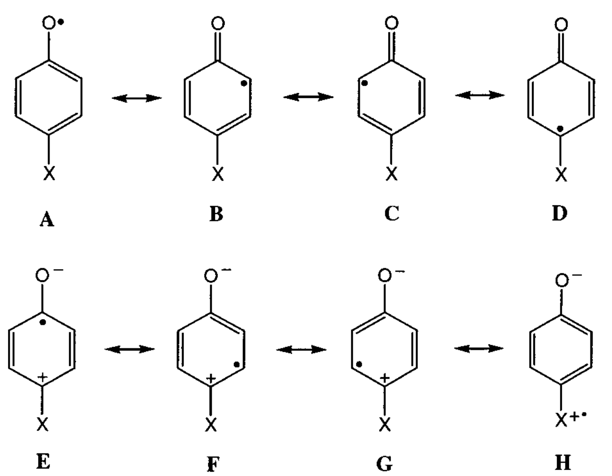


TABLE 2. Substituent Contributions (Δ*D*, kcal mol^{-1}) for Calculating O−H BDE in Phenols

substituent(s)	2	2 and 6	3	3 and 5	4
Me	−1.75	−3.5	−0.5	−1.0	−1.7
Me_3C	−1.75[b]	−4.8	−0.5	−1.0	−1.9
MeO	−0.2[c] (−3.7+3.5)[d]	−3.9	−0.45	−0.9	−4.4
NH_2					−8.1
RS					−1.8
Cl		−0.7			−0.4
Ph					−1.6
PhCH=CH					−3.9
CHO					1.4
COOH					1.5
COOMe					1.3
CN					1.4
NO_2					2.1

[a] Data are referred to $DH°$(PhO−H) = 87.6 kcal mol^{-1}. [b] Assumed equal to the contribution of a single *ortho* methyl substituent. [c] Estimated from data reported in ref 16. [d] The terms −3.7 and +3.5 represent the electronic effect and the contribution due to the intramolecular hydrogen bond, respectively.

tings are well correlated ($r^2 = 0.995$), with the exceptions of the methoxy (OMe) and methylthio (SR) groups.

The good correlation between BDE values and a property characteristic of the radical, such as the hyperfine coupling, suggests that the radical effect is mainly responsible for the magnitude of the O−H bond dissociation enthalpy in the majority of *para* substituted phenols. The fact that electron-releasing substituents containing oxygen and sulfur do not lie on the correlation line is presumably due to the importance of structure **H** where a considerable amount of spin density is delocalized on the heteroatom and therefore removed from the aromatic ring. Structure **H** implies that the reduction of the *meta* proton splittings should be larger than in other phenoxyl radicals where only the polar structures **E**−**G** can be written.

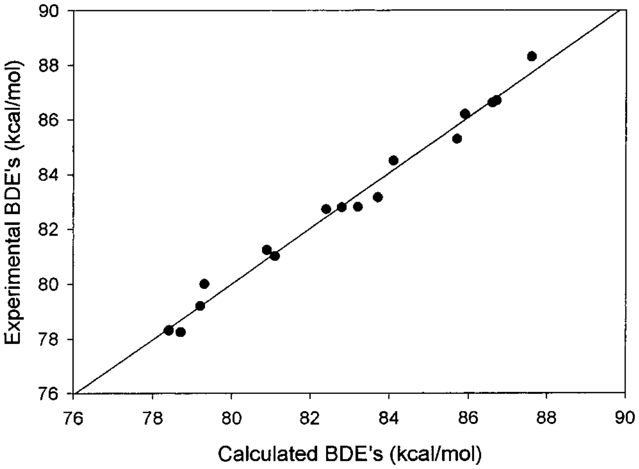


FIGURE 4. Plot of the experimental BDE values vs those calculated using the additivity rule with the substituent contributions reported in Table 2. The value of the slope is 1.01 ($r^2 = 0.985$).

On the basis of the BDE values determined in the present investigation for phenols containing electron-accepting substituents it is possible to extend the list of the additive contributions for the calculation with the group additivity rule of the $DH°$(ArO−H) in polysubstituted phenols. This list, reported in Table 2, is particularly useful because all terms are consistent with each other since they have been determined using the same experimental EPR radical equilibration technique. From the data reported in the Table 2 it is apparent that phenols where both *ortho* positions are substituted with the same group show a peculiar behavior, as the additive contribution for double substitution is not always twice the contribution for single substitution. For instance, with *tert*-butyl groups the effect of double substitution is larger than just twice the contribution of a single substituent. The reason is that only the electronic effect is important in the presence of a single *ortho tert*-butyl group, while both electronic and steric factors contribute to the destabilization of the starting phenol with two *tert*-butyl groups.

Similarly, a single *ortho* methoxy group has an almost negligible effect on the BDE value because the negative contribution due to the electronic effect (−3.7 kcal/mol) is almost totally canceled by the formation of an intramolecular hydrogen bond between the hydroxylic hydrogen and the methoxy group, which stabilizes by 3.5 kcal/mol the starting phenol. Instead, a big change in the BDE value is observed when adding a second *ortho* methoxy substituent since a second hydrogen bond cannot be formed.

The additivity rule provides good estimates of the bond dissociation enthalpies of substituted phenols. In fact, when plotting the experimental BDE values against the calculated ones (see Figure 4) a good correlation ($r^2 = 0.985$) is obtained. Predictions based on the additivity rule should then be considered quite reliable, so that when, for a given phenolic antioxidant, the calculated BDE value differs considerably from the experimental one, this should be taken as an indication that some other kind of effect is operative.[17]

Experimental Section

Materials. 4-X-2,6-di-*tert*-butylphenols (X = CN,[18] Cl,[19] Ph,[20] NO_2,[21] $COOCH_3$,[22] *trans*-CH=CHPh[23]) were prepared

---

(16) De Heer, M. I.; Korth, H. G.; Mulder, P. *J. Org. Chem.* **1999**, *64*, 6969.

(17) Lucarini, M.; Mugnaini, V.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 928−931.

(18) Cohen, L. A. *J. Org. Chem.* **1957**, *22*, 1333−1335.

(19) Ley, K.; Mueller, E.; Scheffler, K. *Chem. Ber.* **1958**, *91*, 2670.

according to literature procedures. All other chemicals were commercially available.

Determination of BDE Values. Deoxygenated benzene solutions containing the phenol under investigation (0.1−0.5 M), an appropriate reference phenol (0.1−0.5 M), and di-*tert*-butyl peroxide (10% v/v) were sealed under nitrogen in a suprasil quartz EPR tube. The sample was inserted in the thermostated cavity of an EPR spectrometer and photolyzed with the unfiltered light from a 500-W high-pressure mercury lamp. The temperature was controlled with a standard variable temperature accessory and was monitored before and after each run with a copper−constantan thermocouple.

The EPR spectra were recorded on a spectrometer equipped with a microwave frequency counter for the determination of the *g*-factors, which were corrected with respect to that of perylene radical cation in concentrated H_2SO_4 ($g = 2.00258$).

The molar ratio of the two equilibrating radicals was obtained from the EPR spectra and used to determine the equilibrium constant, K_1, by introducing in eq 1 the initial concentrations of the two reactants. Initial concentrations were high enough to avoid significative consumption during the course of the experiment.

Relative radical concentrations were determined by comparison of the digitized experimental spectra with computer simulated ones. In these cases an iterative least-squares fitting procedure based on the systematic application of the Monte Carlo method was performed in order to obtain the experimental spectral parameters of the two species including their relative intensities.[6]

Acknowledgment. Financial support from the University of Bologna and MURST (Research project “Free Radical Processes in Chemistry and Biology: Syntheses, Mechanisms, Applications”) is gratefully acknowledged.

JO025755Y

---

(20) Moore, G. G. I.; Kirk, A. R. *J. Org. Chem.* **1979**, *44*, 925.

(21) Cross, G. G.; Fischer, A.; Henderson, G. N. *Can. J. Chem.* **1984**, *62*, 2803.

(22) Pastor, S. D.; Hessel, E. T. *J. Organomet. Chem.* **1987**, 263.

(23) Starnes, W. H.; Myers, J. A.; Lauff, J. J. *J. Org. Chem.* **1969**, *34*, 3404.