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Organochalcogen Substituents in Phenolic Antioxidants

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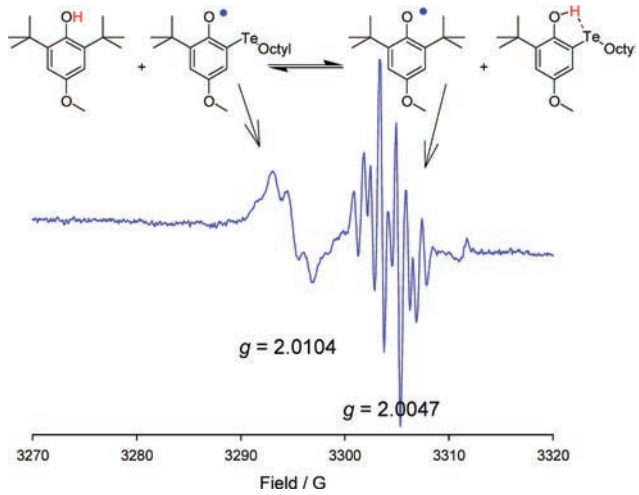
ABSTRACT

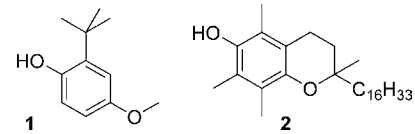


Little is known about the ED/EW character of organochalcogen substituents and their contribution to the O−H bond dissociation enthalpy (BDE) in phenolic compounds. A series of *ortho*- and *para*-(S,Se,Te)R-substituted phenols were prepared and investigated by EPR, IR, and computational methods. Substituents lowered the O−H BDE by >3 kcal/mol in the *para* position, while the *ortho*-effect was modest due to hydrogen bonding (∼3 kcal/mol) to the O−H group.

Phenolic antioxidants such as synthetic butylated hydroxyanisole (BHA, **1**) have been used for more than 60 years to preserve oxidizable products in all kinds of man-made materials.

Similarly, nature has selected a number of phenolic compounds such as α-tocopherol (**2**) to protect living organisms from oxidative stress.[1]

Their antioxidant activity stems from the ability to transfer the phenolic hydrogen to chain-propagating (peroxyl) radicals more rapidly than these would react with the oxidizable material to propagate the oxidative chain.



1 **2**

The rate of formal hydrogen transfer to peroxyl radicals is dictated mainly by the O−H bond dissociation enthalpy (BDE_{OH}).[1] In α-tocopherol as well as in other phenolic

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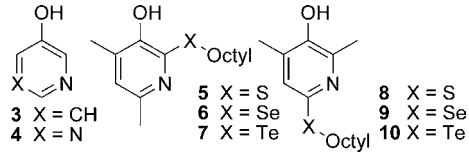
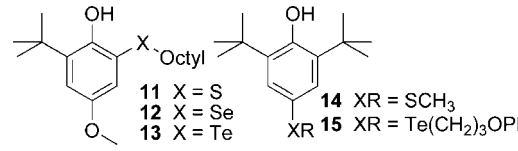
antioxidants, BDE_{OH} is sensitive to the electronic contribution from ring substituents.[2] Thus, *ortho* and *para* electron-donating (ED) groups decrease the BDE_{OH} and increase the reactivity, while the opposite is true for electron-withdrawing (EW) groups.[3] Substituent contributions are approximately additive,[2c] and they are conserved also in ring-modified derivatives such as 3-pyridinols (**3**) and 5-pyrimidinols (**4**).[4] Indeed, knowledge about substituent contributions on the BDE_{OH} has been the key to rational design and development of novel and more effective antioxidants and radical scavengers during the last two decades.



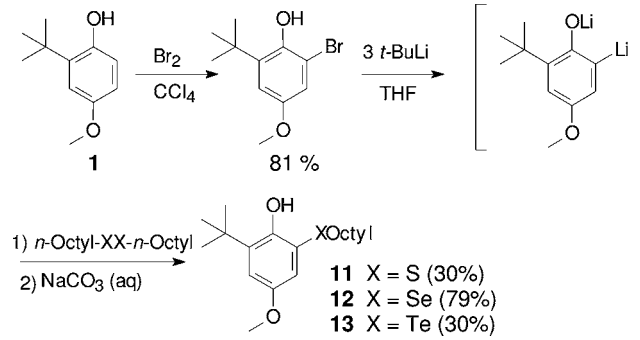
We have for some time tried to design and synthesize chalcogen-substituted regenerable antioxidants, which could perform in a catalytic fashion in the presence of thiol-reducing agents and combine the chain-breaking activity with a GPx-like peroxide decomposing activity.[5] Our work, however, had to proceed on a trial-and-error basis due to the absence of literature data on the contribution of heavy (Se, Te) organochalcogen substituents on BDE_{OH} of phenolic compounds. Knowledge about the ED/EW character of alkyl-(S, Se, Te) substituents or their ability to delocalize an unpaired electron would also be vital in the design of radical conductors based on heavy chalcogens[6] or to rationalize antioxidant effects in complex biological systems.[7]

We have recently reported on pyridinols **5**−**10** bearing *ortho*- or *para*-organochalcogen substituents. Some of them, such as **7**, bearing an *ortho*-alkyltelluro group, showed improved antioxidant characteristics:[8] a feature difficult to rationalize without knowledge about the electronic contribution of alkylchalcogen substituents. Despite its relevance, we were unable to aquire this piece of information by using the well-established method of EPR radical equilibration that has proven to be the most accurate approach for phenolic compounds.[2b,c,3–5] It requires equilibrating compounds that would give rise to persistent aryloxyl radicals or that are sufficiently stable under continuous UV irradiation; none of these requirements were actually satisfied by compounds **5**−**10**.



In order to find out about substituent effects, we synthesized the electron-rich *ortho*-alkylchalcogeno BHA analogues **11**−**13** by bromination of **1**, followed by in situ lithiation of the resulting bromophenol and addition of di-*n*-octyl ditelluride, -diselenide, and -disulfide, respectively (Scheme 1).

Scheme 1. Synthesis of Compounds **11**−**13**



To extend the investigation to some *para* alkyl-(S, Te) groups, we included compound **14**, available from previous studies,[9] and **15**, which could be accessed in 90% overall yield from 2,6-di-*tert*-butylphenol (see Supporting Information). Reference data for *para*-alkyl-Se substituents could be extracted from previous work.[5]

Compounds **11**−**13** were sufficiently electron-rich to produce EPR-detectable concentrations of the corresponding phenoxyl radicals when their 0.01 M solutions in benzene, containing 20−30% di-*tert*-butyl peroxide, were exposed to ambient light inside the cavity of an EPR spectrometer. Very moderate UV irradiation using the unfocused beam from a high-pressure Hg lamp yielded intense spectra (Figure 1), whose deconvolution afforded the hyperfine splitting constants (HSCs) collected in Table 1. Spin delocalization on the chalcogen is witnessed by the increasing *g*-factor on going from S to Te, and by the magnitude of spin coupling with protons in the *ortho*-X-CH_2 moiety. A slight increase in the intensity of UV irradiation caused rapid detelluration of compound **13**, followed by formation of dimeric phenoxyl radicals, while prolonged irradiation was needed to produce similar results with phenols **1**, **11**, and **12** (see Supporting Information).

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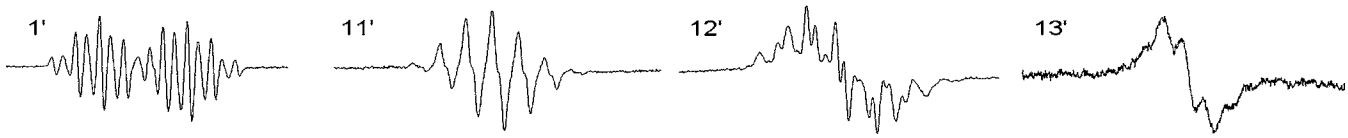

Figure 1. EPR spectra of phenoxyl radicals originated from phenols **1** and **11**−**13** in benzene (with 20% di-*tert*-butyl peroxide) at 298 K.

Table 1. EPR Spectral Parameters for Aryloxyl Radicals from Investigated Compounds in Benzene (containing 20% v/v di-*tert*-butyl peroxide) at 298 K

	HSCs/Gauss			
compound	*ortho*[a]	*meta*	*para*	*g*-factor
1	6.06 (1H)	0.96 (1H); 0.74 (1H)	1.65 (3H)	2.0048
11	1.32 (2H)	1.36 (1H); 0.35 (1H)	1.40 (3H)	2.0053
12	0.79 (2H)	1.32 (1H); 0.35 (1H)	1.41 (3H)	2.0081
13	1.27 (2H)	1.35 (1H); 0.30 (1H)	1.42 (3H)	2.0104
14		1.30 (2H)	2.20(3H)	2.0055
15		∼0.7 (2H)	∼1.5(2H)	2.0122

[a] Coupling with *tert*-bulyl H-nuclei was unresolved (HSC ∼0.1−0.3 G) and led to spectral line broadening.

Table 2. Bond Dissociation Enthalpies of Investigated Phenols (^{U}PhOH) from EPR Equilibrations in Benzene (containing 20% v/v di-*tert*-butyl peroxide) at 298 K[a]

^{U}PhOH	^{R}PhOH	K_{eq}	BDE_{OH} (kcal/mol)[b]
1	TBP	0.78 ± 0.24	80.3 ± 0.2
11	DBHT	0.31 ± 0.10	80.6 ± 0.1
12	TBP	1.89 ± 0.25	
	DBHT	1.25 ± 0.10	79.8 ± 0.1
13	DBHA	0.058 ± 0.016	78.9 ± 0.2
14	DBHA	0.26 ± 0.08	78.0 ± 0.3[c]
15	DBHA	0.093 ± 0.040	78.6 ± 0.3
DBP			81.7[b,2c]

[a] DBP = 2,6-di-*tert*-butylphenol; TBP = 2,4,6-tri-*tert*-butylphenol; DBHT = 2,6-di-*tert*-butyl-4-methylphenol; DBHA = 2,6-di-*tert*-butyl-4-methoxyphenol. [b] Values corrected for revised BDE of phenol (86.7 ± 0.7 kcal; ref 10). [c] Literature value 78.3 kcal/mol (ref 9).

When EPR spectra were recorded on mixtures of compounds **1** or **11**−**15** with variable amounts of reference phenols, rapid equilibration was established.

The resulting EPR spectra were a superimposition of those of the equilibrating phenoxyl radicals, and their analysis allowed determination of the corresponding equilibrium constant, K_{eq}.[2c,3] Since the entropy change associated with the equilibrium is negligible, knowledge of its Gibbs energy change affords the BDE_{OH} of the unknown phenols according to eqs 1−3.[2c,3]

$$^{U}\text{PhOH} + {}^{R}\text{PhO}^{\bullet} \overset{K_{eq}}{\rightleftharpoons} {}^{U}\text{PhO}^{\bullet} + {}^{R}\text{PhOH} \qquad (1)$$

$$\Delta G = \Delta H - T\Delta S = -RT\ln K_{eq} \qquad (2)$$

$$\text{BDE}_{(^{U}\text{PhOH})} = \text{BDE}_{(^{R}\text{PhOH})} - \Delta H \qquad (3)$$

Data collected in Table 2 show that alkyl-S and alkyl-Se groups in the *ortho* position (compounds **11** and **12**) produced only a modest variation in the strength of the phenolic O−H bond as compared with the unsubstituted parent **1**, while alkyl-Te substitution (**13**) significantly decreased the BDE_{OH} (−1.4 kcal/mol). In contrast, *para* substitution with organochalcogen (S or Te) groups lowered the BDE_{OH} by more than 3 kcal/mol as compared with unsubstituted 2,6-di-*tert*-butylphenol: a behavior we attribute to intramolecular H-bonding to chalcogen in *ortho*-substituted phenols. This would increase the BDE_{OH} thereby (partly) compensating for the electron-donating character of organochalcogen substituents.[11] To test this hypothesis, we turned to IR spectroscopy; while BHA (**1**) showed a sharp peak at 3613 cm^{-1} in the O−H stretching region, such a signal was absent in the spectra of *ortho*-substituted derivatives **11**−**13**, which instead showed almost superimposable broad signals at 3375 ± 4 cm^{-1}, indicative of phenolic O−H groups involved in intramolecular H-bonding exceeding ca. 2.5 kcal/mol in strength (see Supporting Information).

To obtain deeper insight into the effects of organochalcogen substituents on the BDE_{OH} of investigated compounds, DFT calculations[12] at the B3LYP/LANL2DZdp level were performed.[13,14] As the BDE-lowering effect of ^{t}Bu groups is difficult to reproduce by theoretical methods,[15] calculations were performed on the corresponding CH_3-substituted compounds, as illustrated in the Supporting Information. Results are compared in Table 3 with the experimentally determined contributions from *ortho*- and *para*-organochalcogen substituents obtained from Table 2, except for the *para*-SeR substitution that was estimated from previous work on selenochromanol analogues.[5a,b]

Calculated substituent contributions reproduced experimental data within ±0.6 kcal/mol, except in the case of *ortho*-TeR, which was overestimated by 1.1 kcal/mol (vide infra). More interestingly, DFT calculations very nicely reproduced the experimental trends: when the chalcogen-containing substituents are in the *para* position, their ability

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Table 3. Calculated Substituent Contribution as ΔBDE_{OH}, Molecule Stabilization Energy (MSE), and Radical Stabilization Energy (RSE), Compared to Experimental ΔBDE_{OH} (kcal/mol)[a]

substituent	ΔBDE_{exp}	ΔBDE_{calc}	MSE_{calc}[b]	RSE_{calc}[c]
ortho-SR	+0.3	−0.3	2.5	2.8
ortho-SeR	−0.5	−0.8	3.4	4.2
ortho-TeR	−1.4	−2.5	3.3	5.8
para-SR	−3.7	−4.3	−0.6	3.7
para-SeR	(−3.4)	−3.5	0.4	3.9
para-TeR	−3.1	−2.9	0.5	3.4

[a] $\Delta BDE = MSE - RSE$.

[b] $ArOH-XMe + C_6H_6 \xrightarrow{MSE} ArOH + C_6H_5-XMe$.

[c] $ArO\bullet-XMe + C_6H_6 \xrightarrow{RSE} ArO\bullet + C_6H_5-XMe$.

to lower the BDE_{OH} decreases on descending the periodic table from S to Te, while the trend is the opposite when the substituents are in the *ortho* position. These trends prompted us to partition the ΔBDE_{OH} values into contributions from the molecule and radical stabilization energies, MSEs and RSEs, respectively (see footnotes in Table 3).[2b] The energies in Table 3 show that X−Me substituents in the *para* position have a nearly constant RSE (≈3.7 kcal/mol), while MSE is weakly negative (destabilizing) for SMe and positive (stabilizing) for SeMe and TeMe. This can be ascribed to an electron-deficient zone along the outer side of the S−, Se−, and Te−CH_3 bond, the so-called "sigma hole" (Figure 2),

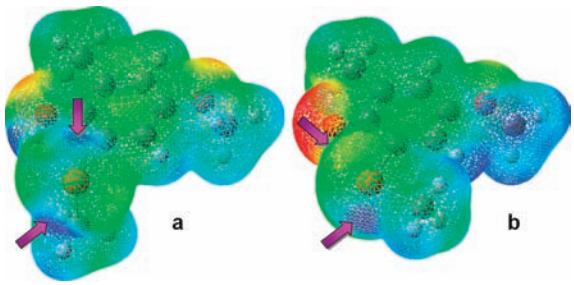

Figure 2. Electrostatic potential on the molecular surface of 2-MeTe-4-MeO-6-MeC_6H_3OH (a) and the corresponding phenoxyl radical (b) (red, negative; blue, positive). Arrows indicate regions of positive electron density (sigma holes) located along the Te−Me and Te−Ar bonds.

which becomes important as the atom size increases (i.e., S < Se < Te).[16] Heavy chalcogen atoms can interact with the π system either with the filled p orbital or with the sigma hole by rotation around the Ar−X bond by about 90°. Actually, optimized geometries show that the dihedral angle between the aromatic ring and the X−Me bond is about 90° in all the phenols, while it is reduced to 0° in the phenoxyl radicals (Figure 2). The perpendicular conformation allows hydrogen bond formation with the phenolic OH in *ortho*-substituted compounds as clearly shown by IR spectra. MSEs can be viewed as summations of the intrinsic effects of substituents, essentially identical for *para* or *ortho* substituents, and the contribution from intramolecular H-bonding, the strength of which, according to data in Table 3, is approximately constant among S−, Se−, and Te−Me groups (≈3 kcal/mol). Surprisingly, in *ortho*-XMe phenols, RSEs show a notable increase while passing from S to Te. We hypothesize that this is due to a favorable electrostatic interaction between the sigma hole on Se and Te atoms and the lone pairs of the phenoxyl oxygen: possibly, the contribution of such an interaction for Te is overestimated by our DFT method, which would explain the poorer agreement between calculated and exprimental ΔBDE_{OH} values for the *ortho*-TeR substituent (vide supra).

Interaction of the sigma hole with the phenol π system (Figure 2a) suggests that S-, Se-, and Te-alkyl substituents would show EW behavior, which becomes ED upon rotation in the phenoxyl radical (Figure 2b). This counterintuitive prediction is confirmed by IR measurements in *para*-XR phenols **14** and **15**. It has been suggested that the O−H stretching frequency for a series of 4-substituted 2,6-di-*tert*-butylphenols depends on the electronic contribution from the substituent.[17] Indeed, using literature data,[17] we found that a plot of ν_{OH} versus the substituents constants σ[18] for the corresponding group in the *para* position is linear (r^2 = 0.996) with ν_{OH} (cm^{-1}) = 3645.3 − 14.5 σ. If the measured values for compounds **14** (ν_{OH} = 3643 cm^{-1}) and **15** (ν_{OH} = 3641 cm^{-1}) are used in this correlation, the resulting σ values for −SR and −TeR substituents are 0.14 and 0.28, respectively, confirming the predicted EW behavior in the parent phenols.[19]

In conclusion, B3LYP/LANL2DZdp calculations very nicely reproduced experimental findings and could be a valuable tool to estimate the role of organochalcogen substituents when experimentally not accessible. We believe that the experimental thermodynamic and spectroscopic data obtained in this investigation will significanly aid the rational design of organochalcogen-substitued functional phenols.

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Supporting Information Available: Synthesis procedures, spectroscopy, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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