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Role of Noncovalent Sulfur···Oxygen Interactions in Phenoxyl Radical Stabilization: Synthesis of Super Tocopherol-like Antioxidants

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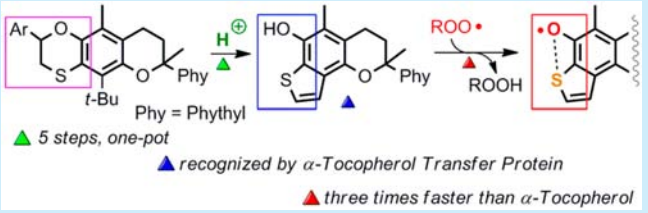
Supporting Information

ABSTRACT: Noncovalent sulfur···oxygen interactions can increase the stability of chalcogen *ortho*-substituted phenoxyl radicals. This effect contributes to transforming the 7-hydroxybenzo[*b*]thiophene moiety in a privileged structural motif to enhance the activity of phenolic antioxidants. A cascade of five consecutive electrophilic reactions occurring in one pot afforded potent and biocompatible α-tocopherol-like antioxidants.



Phenols (ArOH) are probably the most important class of natural and synthetic antioxidants used for the protection of manmade items and living tissues from oxidation.[1] Nature selected α-tocopherol (α-TOH), the main component of vitamin E (Vit E), as the most potent lipophilic chain-breaking antioxidant for the protection of cell membranes and LDL from autoxidation.[2] This ability depends on the easy transfer of an H atom from α-TOH to, typically, peroxyl radicals (ROO•) with formation of a relatively safe phenoxyl radical (α-TO•). This can be reduced by various reductants (such as ascorbate, vitamin C) in a synergetic red-ox cycle.[3] Ingold and co-workers studied the stereoelectronic issues that make α-TOH the model for lipophilic antioxidants, and their pioneering achievements inspired improvements on this topic. Considering the key H• transfer process, the lower the bond dissociation energy (BDE) of the phenolic O−H, the higher is the rate constant (k_{inh}) of the reaction with ROO•.[4] Thus, any stabilization of the starting phenol, for example, the involvement of the phenolic OH in a H bond,[5] will hamper the process, while any stabilization of the Ar−O• will facilitate it. The transformation of Ar−OH into Ar−O• means transforming an electron-donating (ED) group into an electron-withdrawing (EW) group.[5e] Therefore, ED groups on the aromatic ring (i.e., as in α-TOH) strongly stabilize the Ar−O•, facilitating the H• transfer.[5] The *p*-alkoxy group plays a relevant role, but resonance stabilization requires a correct conformation; i.e., one lone pair of the alkoxy oxygen should be parallel to the aromatic π orbitals. Actually, this situation takes place when the Ar−O−R dihedral angle is near to 0°, a situation that is facilitated by the alkoxy oxygen inserted in a benzo-fused six-membered ring (as in α-TOH) or, even better, in a five-membered ring as in the dihydrobenzo[*b*]-furanol (**DhyBF**) (Figure 1).[5,6]

Accordingly, k_{inh} increases from 5,7,8-trimethyl-6-hydroxychromane (as in α-TOH) to dihydrobenzo[*b*]furanol (**DhyBF**) since the five-membered ring is almost coplanar with the aromatic ring (Figure 1).[5,6] Several years ago, Ingold also demonstrated that benzo[*b*]furanol (**BF**), despite its complete planarity, shows an important decrease (roughly 10 times) of the H• transfer ability.[7] This was explained by considering that aromatization reduced the ED ability of the endocyclic O atom.[7] Thus, in the design of new phenolic antioxidants inspired by α-TOH, aromatic benzo-fused heterocyclic systems have been barred since a decreasing ability in the stabilization of the Ar−O• is expected.[8] We demonstrate here that the situation changes with benzo[*b*]thiophenes. Introduction of chalcogens in the skeleton of phenolic antioxidants and, in particular, in that of α-TOH can offer the opportunity to link the chain-breaking antioxidant to the (catalytic) hydroperoxide quencher ability of chalcogens (mainly Se and Te).[9] During our research, we pointed out a peculiar behavior of sulfur-substituted phenolic antioxidants

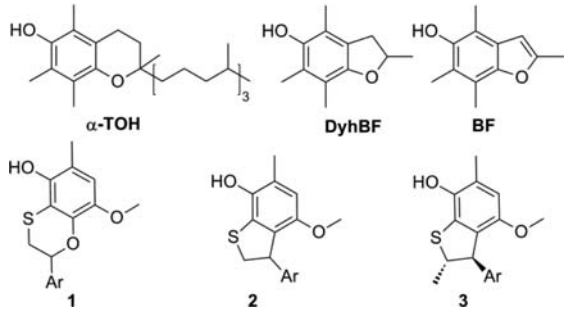


Figure 1. Benzo-fused phenolic antioxidants.

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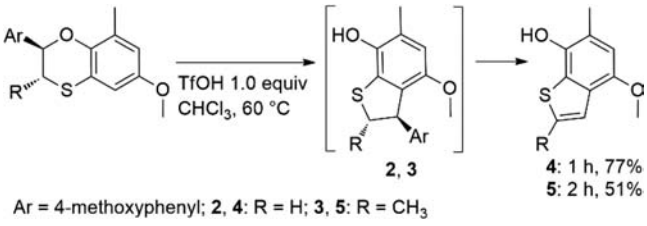
bearing the sulfur atom *ortho* to the phenolic OH and inserted in a benzoxathiine heterocyclic system. In these derivatives, the sulfur is a poor acceptor of intramolecular H bonds,[10] while it maintains its ED character and the ability of stabilizing Ar−O•. This allowed us to propose a rationale for the post-translational cysteine−tyrosine linkage in the galactose oxidase (GAO) active site[11] and to prepare, in several steps and low overall yields, potent antioxidants[12] (like compound **1** Figure 1) with k_{inh} equivalent to that of α-TOH (k_{inh} = 3.2 × 10^6 M^{-1} s^{-1}). Recently, exploiting a procedure based on an acid-mediated benzoxathiine−dihydrothiophene rearrangement (Scheme 1),

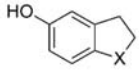
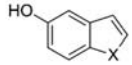
Scheme 1. From 1,4-Benzo[*b*]oxathiines to 7-Hydroxybenzo[*b*]thiophenes



we efficiently prepared 7-hydroxydihydrobenzo[*b*]thiophenes like **2** and **3** (Figure 1) showing, in turn, high k_{inh} (~1.4 × 10^6 M^{-1} s^{-1}).[13] While studying the benzoxathiine−dihydrothiophene rearrangement, we discovered that under harsher acid conditions, i.e., using triflic acid (TfOH) as promoter, dihydrobenzo[*b*]thiophenes **3** and **4** are transformed into benzo[*b*]thiophenes **4** and **5**, which can be also directly obtained from the benzoxathiine derivatives without isolation of intermediates **2** and **3** (Scheme 1).

Despite being synthetically useful, taking into consideration the previously reported evidence on the dihydrobenzo[*b*]furan vs benzo[*b*]furan pair,[7] the transformation reported in Scheme 1 appeared to be detrimental for antioxidant activity. Surprisingly, measured k_{inh} of **4** and **5** were up to three times higher than those of the corresponding dihydro precursors **2** and **3** (see Table 2). Since a benzo[*b*]thiophene is, at least, as "aromatic" as a benzo[*b*]furan, a rationale for this result requires envisaging some additional effect responsible for the extra stabilization of the Ar−O• involving the sulfur atom. We initially evaluated the BDE(OH) of these phenols by theoretical calculations.[14] Phenols **4** and **5** showed identical BDE(OH) values (74.6 kcal/mol) that were 3.2 kcal/mol lower than **2** or **3** (77.8 kcal/mol) and 1.0 kcal/mol lower than 2,2,5,7,8-pentamethylchroman-6-ol (PMC, a "calculation friendly" analogue of α-TOH) (75.6 kcal/mol). The good agreement between calculated BDE(OH) and kinetic results encouraged us to investigate at this level of theory the BDE(OH) of parent 5- and 7-hydroxybenzo-fused five-membered heterocycles containing O, S, and Se[15] atoms (see Table 1). For 5-hydroxy derivatives (i.e., the endocyclic heteroatom is *para* to the OH), aromatization has a negative impact on the BDE(OH), in particular for furans, in line with Ingold's result.[7] On the other hand, for 7-hydroxy derivatives (i.e., the endocyclic heteroatom is *ortho* to the OH), aromatization has either no effect, as for oxygen, or a BDE-lowering effect as for sulfur and selenium. Obviously, calculated BDEs reported in Table 1 depend on several factors contributing to the stabilization of the parent phenols and of the phenoxyl radicals (Figures 5SI and 6SI). However, focusing on the relative stability of phenoxyl radicals, it appears even

Table 1. Calculated ArO-H BDE and Most Positive σ-Hole Electrostatic Potentials on S and Se Atom

substrate	BDE[a]			$V_{s,max}$[a,b] ArOH / ArO•	
	O	S	Se	S	Se
	79.5	81.1	81.9	24 / 44	32 / 47
	84.2	84.7	84.9	37 / 50	41 / 54
	84.3	83.3	83.4	26[c] / 38	31[c] / 41
	84.3	82.1	82.6	36[c] / 44	40[c] /48

[a]kcal/mol. [b]Calculated on an isodensity surface corresponding to 0.005 au by Multiwfn software (ref 14c). [c]Relative to the most stable conformer with the O−H bond pointing opposite to S or Se atom, as shown in Figure 2 (bottom). See the Supporting Information for details.

more clear that aromatization causes an "unexpected" stabilization of the *o*-phenoxyl radical. Enthalpy differences between the phenoxyl radicals of 5- and 7-hydroxy isomers show that *o*-dihydro radicals are less stable than *para* radicals (up to 3.6 kcal/mol for furans), while *ortho* "heteroaromatic" radicals are more stable than *para* radicals (more than 3 kcal/mol for thiophenes and selenophenes (Figure 7SI)).

We hypothesized this was the fingerprint of an intramolecular interaction between an electron-deficient area on the surface of the covalently bonded chalcogen (S or Se) and the negative surface of the O atom.[16] Analysis of the electrostatic potential surfaces of the investigated compounds indicated, on the sulfur and selenium atoms, the presence of σ-holes[17] as two regions of positive potential along the outer sides of the carbon−chalcogen σ-bonds (Figure 2 and Figure 4SI).

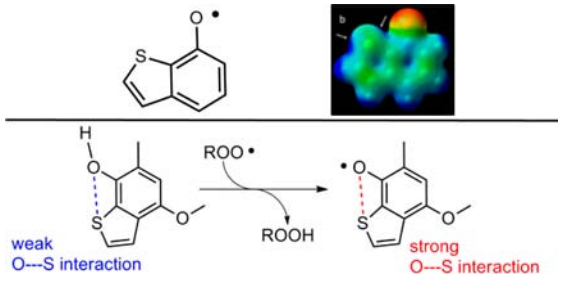


Figure 2. (Top) Molecular electrostatic potential showing the σ-hole position (blue, positive potential; red, negative potential). (Bottom) Preferential stabilization of the phenoxyl radical by the interaction between the sulfur σ-hole and the oxygen atom.

Quantitative analysis of electrostatic potential surfaces,[14c] reported in Table 1, showed that the σ-hole increased (i) with the atomic number of the chalcogen atom, (ii) with aromatization, and (iii) by passing from phenols to phenoxyl radicals. These observations agree with the known determining factors of σ-hole magnitude,[17] which are size and polarizability of the chalcogen atom and electron density removal, due to the inclusion into an aromatic system or to the presence of

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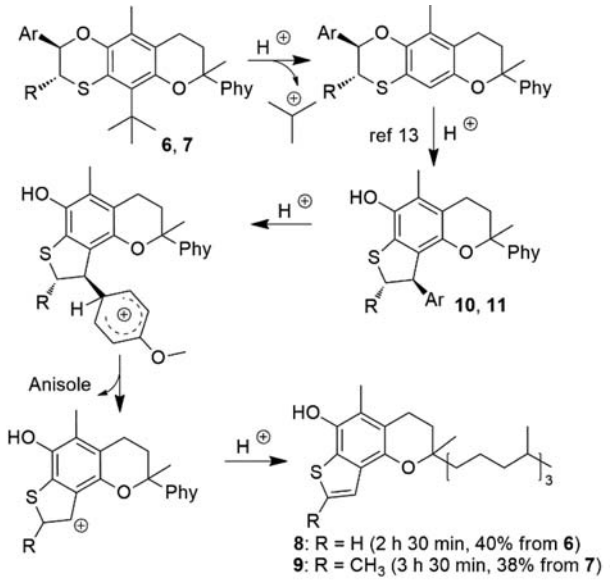
electron-withdrawing groups. Figure 2 (top) shows that one σ-hole on the S atom points toward the phenoxyl oxygen, whose surface is largely negative. In recent years, noncovalent sulfur··· oxygen interactions have been used to rationalize the receptor–drug binding[18] or the preferred conformation of polythiophenes in organic electronic devices,[19] even though, to the best of our knowledge, the stabilization of a radical intermediate is unknown. Actually, alignment between the σ-hole and the oxygen lone pair is not optimal in our systems for an oxygen··· sulfur σ-hole interaction. However, NBO perturbation theory analysis revealed a weak interaction between an oxygen lone pair and the $\sigma^*_{(S-C2)}$ in the 7-benzothiophenoxyl radical (0.16 and 0.18 kcal/mol for α and β spin sets, respectively). This interaction is absent in the 7-benzofuranoxyl radical. Likewise, in the structurally related 2-acetylthiophene, the occurrence of a weak chalcogen bond is invocated to justify the preference for the s-*cis* conformation.[20] Upon closer inspection, several other examples of "directionally unfavorable" intramolecular interactions are available in literature.[18,19] Additionally, an oxygen··· sulfur σ-hole interaction is also present when approaching parent phenoxyl radical and thiophene, a simplified intermolecular model that we investigated to support our hypothesis following the appreciated suggestion of a reviewer (Figure 8SI).

Thus, reasonably, the high reactivity and low BDE(OH) of **5** and **6** can be also attributed to a weak S···O chalcogen bond, whose strength increases upon passing from the parent phenol to the phenoxyl radical (Figure 2 (bottom)). These results prompted us to explore the preparation of a family of super Vit E like phenolic antioxidants by properly introducing the benzo[*b*]thiophene structural motif in the α-TOH skeleton (Scheme 2). We started studying the building of the chroman

Scheme 2. Mechanism and Synthesis of Tocopherols Containing the Benzo[*b*]thiophene Structural Motif



ring by cross-cyclic addition to the suitable phenol (Scheme 1SI).[21] Thus, *tert*-butylation of 2-methylhydroquinone followed by reaction with phythol allowed the regioselective preparation of the 2-phythylchromane-substituted phenol. Using our well-established methodology,[8b,11−13] the phenol was transformed into benzoxathiines **6** and **7** as suitable substrates for the acid-promoted transposition process (Scheme 1SI). However, the *tert*-butyl group, inserted to ensure the regioselective closure of the chromanic ring, should be removed to allow the dihydrobenzothiophene ring closure. Additionally, the acid conditions required for transposition should preserve the chroman ring. To our satisfaction, we verified that both achievements (i.e., de-*tert*-butylation and chroman ring conservation) could be accomplished under the reaction conditions effective for the transposition (Scheme 2). Thus, by reacting oxathiines **6** and **7** with 1 equiv of TfOH in $CHCl_3$ at 60 °C, we observed the initial formation of dihydro derivatives **10** and **11** followed by benzo[*b*]thiophenes **8** and **9**. Modulating the reaction times, it was possible to isolate mixtures largely enriched in the required thiophenes (**8** vs **10** or **9** vs **11**;[22] see the Supporting Information for details). Remarkably, the formation of benzo[*b*]thiophenes **8** and **9** is the result of five consecutive electrophilic events (i.e., de-*tert*-butylation, benzoxathiine ring opening, dihydrobenzothiophene ring closure, retro-alkylation, and deprotonative aromatization) occurring in one pot (Scheme 2). As expected, the chromanic and the thiophenic fused rings together in the right position ensured a remarkable antioxidant activity with k_{inh} of **8** and **9** up to three times higher than those of **10**, **11**, and α-TOH (Table 2).

Table 2. Reactivity toward Peroxyl Radicals (k_{inh}) and Affinity to α-Tocopherol Transfer Protein (α-TTP)

substrate	k_{inh} /10^6[a] (M^{-1} s^{-1})	R[b]
2	1.5[c]	
3	1.4[c]	
4	5.0	
5	5.9	
10	3.2	
11	2.9	
8	7.4	1.8
9	9.8	0.8
all-rac-α-TOH	3.2[d]	1

[a]Measured by studying the inhibited autoxidation of styrene in PhCl, initiated by AIBN at 30 °C. The stoichiometry of radical trapping was ~2 (see the Supporting Information). [b]$R = K_d$ (ligand)/K_d (*all-rac*-α-TOH). [c]From ref 13. [d]From ref 6a.

Eventually, we measured the binding of α-tocopherol transfer protein[23,24] (α-TTP) to **8** and **9** to verify whether introduction of the benzo[*b*]thiophene moiety on the α-TOH skeleton is a tolerable modification at the biological level.

Thus, we measured the tryptophan fluorescence quenching caused by the enzyme–substrate interaction. As discussed in the Supporting Information, due to the known dependence of K_d on experimental conditions,[25] we decided to express the dissociation constant of the antioxidant molecules with respect to that of natural *all-rac*-α-TOH.[26] The dissociation constant ratio, *R*, reported in Table 2, shows how the insertion of an unsubstituted (**8**) or a 2-methyl-substituted benzo[*b*]thiophene (**9**) moiety in the α-TOH skeleton was well tolerated, resulting in similar binding affinities.

7-Hydroxybenzo[*b*]thiophene is a privileged structure for the construction of potent Vit E like phenolic antioxidants. A noncovalent interaction between the ArO$^\bullet$ group and the sulfur σ-hole ensures extra stabilization of the phenoxyl radical that lowers the phenolic BDE(O–H) and increases the reactivity toward ROO$^\bullet$. A smart, one-pot procedure consisting of a

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cascade of five consecutive electrophilic transformations, occurring one pot, provided two benzo[*b*]thiophene tocopherols, perfectly recognized by α-TPP, with k_{inh} three times higher than that of α-TOH.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02557.

Experimental procedures, including synthesis of intermediates, k_{inh} and K_d measurement, and calculation details (PDF)

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Notes

The authors declare no competing financial interest.

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