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Boosting effect of *ortho*-propenyl substituent on the antioxidant activity of natural phenols

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ABSTRACT

Seven new antioxidants derived from natural or synthetic phenols have been designed as alternatives to BHT and BHA antioxidants. Influence of various substituents at the *ortho*, *meta* and *para* positions of the aromatic core of phenols on the bond dissociation enthalpy of the ArO–H bond was evaluated using a DFT method B3LYP/6-311++G(2d,2p)//B3LYP/6-311G(d,p). This prediction highlighted the *ortho*-propenyl group as the best substituent to decrease the bond dissociation enthalpy (BDE) value. The rate constants of hydrogen transfer from these phenols to DPPH· radical in a non-polar and non-protic solvent have been measured and were found to be in agreement with the BDE calculations. For *o*-propenyl derivatives from 2-*tert*-butyl-4-methylphenol, BHA, creosol, isoeugenol and di-*o*-propenyl *p*-cresol, fewer radicals were trapped by a single phenol molecule, i.e. a lower stoichiometric number. Reaction mechanisms involving the evolution of the primary phenoxyl radical ArO· are proposed to rationalise these effects.

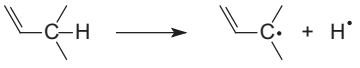
1. Introduction

Many authors have demonstrated the beneficial effects of antioxidants for foodstuff preservation and in human health since it is clearly established that lipid peroxidation is responsible for the rancidification of fats and oils as well as for age related degenerative diseases (Halliwell, Aeschbach, Löliger, & Aruoma, 1995; Hussain et al., 2003). In contrast, less work has been devoted to antioxidants for the preservation of flavours and fragrances although several families of raw materials such as terpenes, ethers or aldehydes are known to be very sensitive towards oxidation while they are very common in end-use formulations (Dupont, 1940; Hagvall et al., 2007; Marteau, Ruyffelaere, et al., 2013). Indeed, they suffer from an autoxidation process by molecular oxygen $^3O_2$ accelerated by metal traces, heat or light (Denisov & Afanas'ev, 2005; Marteau, Ruyffelaere, et al., 2013). This degradation phenomenon has dramatic consequences on the functional properties of the final product, since it can induce bad odour, colour and/or pH modifications, as well as the formation of allergenic molecules. To avoid autoxidation and accordingly product degradation, preservative agents are necessary. Phenol derivatives are the most widely used antioxidants in food and fragrances. They act as chain-breaking antioxidants by transferring a hydrogen atom to peroxyl radicals (Eq. (1) with Z = ArO) at a rate higher than the propagation reaction (Eq. (1) with Z = allyl or carbonyl) converting thus peroxyl ROO· or acylperoxyl RC(O)OO radicals into non-radical products (Denisov & Afanas'ev, 2005; Lucarini & Pedulli, 2010).

$$ROO^{\cdot} + Z{-}H \xrightarrow{K_{inh}} ROOH + Z^{\cdot} \quad (1)$$

Generally speaking, efficient antioxidants exhibit low bond dissociation enthalpy (BDE) of the phenolic bond (Eq. (2)) compared to that of the allylic (Eq. (3)) and aldehydic (Eq. (4)) bonds making them competitive in propagation reactions (Burton & Ingold, 1986; Denisov & Khudyakov, 1987; Hussain et al., 2003).

$$ArO{-}H \rightarrow ArO^{\cdot} + H^{\cdot} \quad (2)$$



(3)

(4)

Moreover, a phenolic antioxidant is effective because the reaction of peroxyl radicals with O—H bonds is much faster than that with

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C—H bonds. However, some of the most popular synthetic phenolic antioxidants, such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), are or are about to be banned because of their toxicity on animals (Ito, Fukushima, Hagiwara, Shibata, & Ogiso, 1983; Saito, Sakagami, & Fujisawa, 2003). Industrial suppliers of foods, fragrances and cosmetics are thus forced to find substitutes for these synthetic antioxidants. A first way to circumvent this issue is to resort to natural antioxidants (Amorati & Valgimigli, 2012; Goupy, Dufour, Loonis, & Dangles, 2003; Rice-Evans, Miller, & Paganga, 1996; Sanchez-Moreno, Larrauri, & Saura-Calixto, 1998; Villaño, Fernández-Pachón, Moyá, Troncoso, & García-Parrilla, 2007). However, these phenols suffer from two main drawbacks: they are relatively costly and some of their oxidation products are coloured which is unacceptable for applications such as fine perfumery (Dangles, Fargeix, & Dufour, 1999). Another way would consist in using some phenolic flavour and fragrance molecules themselves as antioxidants (Marteau, Nardello-Rataj, Favier, & Aubry, 2013; Suja, Jayalekshmy, & Arumughan, 2004). For instance, the antioxidant properties of eugenol and isoeugenol have already been reported (Brand-Williams, Cuvelier, & Berset, 1995). Finally, a third approach would be to simply develop new phenolic antioxidants with high hydrogen transfer capacity on the basis of theoretical effects of various substituents that could be easily grafted onto phenols (Johansson et al., 2010; Wijtmans et al., 2003).

We followed herein this latter strategy by modifying the chemical structure of some phenolic flavours and fragrances so as to increase their antioxidant activity. The design of such new antioxidants consisted of three steps: (1) selection of fragrant phenols which exhibit, or could exhibit after chemical modification, a significant antioxidant activity (Wijtmans et al., 2003), (2) identification of the structural parameters able to decrease the BDE of ArO—H bond and to stabilise the phenoxyl radical and (3) grafting onto the selected phenols the most relevant substituent, chosen among those frequently encountered in fragrant phenols. Thus, seven new antioxidants derived from common phenols were designed by grafting a propenyl group onto the phenyl core. The rate constants of hydrogen transfer from these phenols to the DPPH· radical and the number of H atoms that can be donated by each phenol were compared to those of the starting phenols.

2. Materials and methods

2.1. Materials

Chemicals used in this work included *p*-cresol **1** (IFF, 99%), 2-*tert*-butyl-4-methylphenol **2** (Sigma–Aldrich, 99%), BHA **3** (Sigma–Aldrich ⩾98%), guaiacol **4** (Fluka, ⩾98%), creosol **5** (IFF, 98%), isoeugenol **6** (IFF, 98%), alkyl bromide (Alfa Aesar, 99%), K_2CO_3 (Carlo Erba, 99%), acetone (Verbiese, 99%), KOH (Sigma–Aldrich, 98%), methanol (Sigma–Aldrich, Chromasolv®, 99.99%), petroleum ether (Verbiese), TFA (Alfa Aesar, 99%), hexamethylenetetramine (Fluka, 99.5%), THF (Acros ⩾99%, distilled before use), triphenylphosphine (Alfa Aesar, 99%), ethyl bromide (Fluka, 98%). DPPH· (Sigma–Aldrich, 97%), toluene (Sigma–Aldrich, Chromasolv®, 99.9%), ethyl acetate (Verbièse, 99%), octane (Sigma–Aldrich, 99%) and decanal (IFF, 97%).

2.2. BDE calculation

The so-called BDE of the O—H bonds in a phenol, which corresponds in fact to the bond dissociation enthalpy, is given by the difference between the enthalpy of the phenoxyl radical (plus that of the hydrogen atom) and that of the starting phenol as described by Eq. (5).

$$\begin{aligned} &\mathrm{ArO{-}H} + \mathrm{X}^{\cdot} \xrightarrow{\mathrm{BDE}} \mathrm{ArO}^{\cdot} + \mathrm{X{-}H} \\ &\mathrm{BDE(ArO{-}H)} = H_f^0(\mathrm{ArO}^{\cdot}) + H_f^0(\mathrm{H}^{\cdot}) - H_f^0(\mathrm{ArO{-}H}) \end{aligned} \tag{5}$$

All the calculations were performed with Gaussian 03 packages (Szymusiak & Zielinski, 2003). The geometries of all the parent molecules were firstly optimised with the PM3 method and then the DFT one by using the B3LYP/6-311G(d,p) basis set. The first method was used to speed up the convergence of the optimisation by the second one. The frequency has been calculated to verify that the structure corresponds to an energy minimum. Moreover, the zero-point energy (ZPE) was taken into account to correct the BDE values. Geometries from this method were used as inputs to the final energy B3LYP/6-311G ++(2d,2p) calculation. For species having several conformers, all of them were investigated. The conformer with the lowest electronic energy was used in this work. For radicals, the optimisation also used the PM3 step plus the final UB3LYP/6-311G(d,p) method. Geometries were then used as inputs to the final UB3LYP/6-311G++(2d,2p) calculation. Calculations were performed in toluene. The method is described as B3LYP/6-311++G (2d,2p)//B3LYP/6-311G(d,p).

2.3. General synthesis of *o*-propenyl phenols

The *o*-alkylation of phenols **1**–**6** by the alkyl bromide (1.1 equiv.) was carried out with an excess of K_2CO_3 (10 equiv.) in refluxing acetone giving the allylic ether A. The Claisen rearrangement of **A** was performed by heating at 220 °C for 2 h without solvent under microwaves giving phenol **B**. Isomerization was carried out by heating at 150 °C for 3 h under microwaves with an excess of KOH in methanol (10 equiv.) (Eq. (6)). The microwaves apparatus is a Biotage initiator device (Biotage, Uppsala, Sweden).

(6)

Analytical thin layer chromatography (TLC) was performed on silica gel plates (Merck $60F_{254}$) visualised with a UV lamp (254 nm). Flash chromatography was performed on silica gel (40–60 mesh) using a mixture of ethyl acetate and petroleum ether (1:9 *v*/*v*). For the synthesis of phenol **1PP**, the starting phenol was the *o*-allylphenol **1PA** and isomerization was performed by increasing the microwaves reaction time.

2.4. Determination of the rate constants for hydrogen transfer from phenols to DPPH· radical

Solutions of DPPH· were prepared in toluene at a concentration of *ca.* 5 mM by sonicating the mixture until all DPPH· crystals were dissolved. The solutions were then maintained under argon at 20 °C. For phenols, solutions were also prepared in toluene at a concentration of *ca.* 50–200 mM by sonicating until all crystals were dissolved. Typically, 10–500 μL of the phenol solutions were added to 500 μL of DPPH· solution in a glass reactor of 50 mL equipped with a UV fibre containing 20 mL of deoxygenated solvent maintained at 20 °C. The hydrogen-transfer reaction from phenol to DPPH· radical was accompanied by a change in the UV–visible spectrum and was monitored at 517 nm with a Varian spectrophotometer (Cary 50, 10 pts/s). The loss of DPPH· absorbance in the presence of an excess of phenol follows pseudo-first order kinetics. The rate constants were determined for at least five different phenol concentrations plotting k_{DPPH} *versus* [phenol]. It is the case for phenols **2**, **3**, **5**, **6**, **8** and **2P**, **3P**, **5P**, **6P**. In the case of all other phenols (**1**, **4**, **7** and **1P**, **1PP**, **4P**), the reaction with DPPH· radical is very fast and the rate constants were determined by using stoichiometric conditions at 517 nm considering second-order kinetics ([DPPH·]/[tocopherol] = 1/1). For these phenols, solutions were prepared in toluene at a concentration of *ca.* 5 mM by sonicating until all crystals were dissolved. Values of the rate constants are given in the Supporting information (see Table S1). Under these conditions, ε and ε' values are 11 800 L mol^{-1} cm^{-1} and 24 L mol^{-1} cm^{-1} for DPPH· and DPPH-H respectively.

2.5. Determination of the stoichiometric number for the reaction of phenols with DPPH·

Solutions of DPPH· were prepared in toluene at a concentration of *ca.* 0.1 mM by sonicating the mixture until all DPPH· crystals were dissolved. The solutions were then maintained under argon at 20 °C. For phenols, solutions were also prepared in toluene at a concentration of *ca.* 5–50 mM by sonicating until all crystals were dissolved. Typically, 10–30 μL of the phenol solutions were added to 2.8 mL of a DPPH· solution in a UV cell stirred and maintained at 20 °C. The absorbance change was monitored at 517 nm by using the UV–Visible Cary 60. Final A_f and initial A_0 absorbances were used to determine the stoichiometric number σ according to Eq. (14). Final absorbances were collected when constant values were reached for at least 30 min. Values of the stoichiometric number σ are given in the Supporting information (see Table S2).

3. Results and discussion

3.1. Design and synthesis of new phenolic antioxidants

To design new effective phenolic antioxidants, it is necessary to identify which substituent and which position can improve the antioxidant activity of the starting phenol. As a rule of thumb, phenolic compounds with low ArO—H BDE are efficient as antioxidants (Wright, Johnson, & DiLabio, 2001; Zhang, 1998). They can easily transfer a hydrogen atom to radicals and thus inhibit the chain propagation step induced by the peroxyl ROO· or acylperoxyl RC(O)OO· radicals involved in terpene and aldehyde oxidation, respectively (Lucarini & Pedulli, 2010). BHA, BHT and α-tocopherol which have low BDE values (80.0, 79.9 and 77.1 kcal mol^{-1} respectively) (Lucarini & Pedulli, 2010) are the most frequently encountered antioxidants in perfumery. However, BHA is already banned, BHT is likely to be and α-tocopherol is much more expensive than these two synthetic antioxidants.

Knowledge of BDEs has been accumulated over the past 20 years. More precisely, experimental methods, such as electrochemical measurements, radical equilibrium electron paramagnetic resonance REqEPR method, pulse radiolysis and quantum chemical calculations using large basis sets have been combined. Perez-Gonzalez et al. and Leopoldini et al. published interesting work concerning BDE calculation of polyphenols (Leopoldini, Russo, & Toscano, 2010; Perez-Gonzalez, Rebollar-Zepeda, Leon-Carmona, & Galano, 2012). As explained by Lukes et al., Moller–Plesset (MP) methods significantly underestimate substituent effects (Klein & Lukes, 2006; Klein, Lukes, Cibulkova, & Polovkova, 2006) whereas DFT methods reflect the effect of substituents on BDE satisfactorily. We can notice that if we compare our theoretical calculated BDE values with the literature, we can find some discrepancies. For example, in the case of phenol, the DFT calculation gives 82.2 kcal mol^{-1} while the most reliable gas-phase BDE reported in the literature by Mulder et al. is 86.7 kcal mol^{-1} (Mulder et al., 2005). Moreover, other theoretical BDE values of phenol were found such as 90.3 kcal mol^{-1} (Klein & Lukes, 2006). Thereby, these theoretical results are basis set and solvent dependent (Brinck, Haeberlein, & Jonsson, 1997). However, it is known that a systematic underestimation of about 5 kcal mol^{-1} can arise from the DFT calculation but it is generally reliable for predicting substituent effects on O—H BDE. Hence, it is better to consider the ΔBDE values instead of the theoretical BDEs of phenols as reported in Table 1. These values are consistent with published theoretical values except for OMe substituent (Table 1, entry 12) which is underestimated. Theoretical values for phenolic antioxidants are also consistent with experimental values reported by Lucarini and Pedulli (2010) (r^2 = 0.97) and theoretical data found in literature (Table 2).

The effect of electron-donating and electron-withdrawing substituents was studied in numerous experimental and theoretical works for more than 20 years, from the early 1990s (Lucarini & Pedulli, 2010; Wright et al., 2001). In a previous work, we have also shown that electron-donating groups decrease the BDE values, in particular at the *ortho*- or *para*-positions (Marteau, Nardello-Rataj, et al., 2013). In this work, we have extended the study by calculating with the same and more appropriate DFT method described as B3LYP/6-311++G(2d,2p)//B3LYP/6-311G(d,p), the BDE of ArO—H bond of phenol itself and of 12 phenol derivatives bearing different substituents at the *ortho*-, *meta*- or *para*-positions frequently encountered in natural phenols (*i.e.* methyl, ethyl, methoxy, allyl, propenyl) or in synthetic antioxidants (*i.e. tert*-butyl). Results are given in Table 1.

Comparison of entries 1, 2, 5, 6 and 11 confirms that the decrease of the BDE values is even more important when the electro-donating substituent effect is stronger (Wright et al., 2001). The *ortho*-effect includes steric effects and intramolecular hydrogen bonding. Moreover, substituents in *meta*-position are really unfavourable (see Table 1, entries 3, 9 and 12) compared to substituents in *ortho*- (see Table 1, entries 2, 8 and 11) and *para*-positions (see Table 1, entries 4, 10 and 13) and, accordingly, the BDE increases. This unfavourable effect has already been shown by some authors (Chandra & Uchimaru, 2002; Zhang, Sun, & Chen, 2001). Finally, the BDE of phenols substituted by a propenyl group (entries 8, 9, 10) is substantially lower than the one of phenol substituted by an allyl group (entry 7) because the conjugation of the propenyl with the aromatic ring allows a better delocalisation of the free electron of the phenoxyl radical.

Since the antioxidant activity of phenols generally increases when the BDE value of the phenolic OH bond decreases and when the ionisation potential value is relatively high (Klein & Lukes, 2006), we conducted the evaluation of the antioxidant properties of 7 phenols (**1P** to **1PP**), including 1 or 2 propenyl groups at the *ortho* or *para* positions. These compounds were synthesised from

Table 1
Contributions to the BDE values of the ArO–H bond of phenols in toluene bearing different *ortho* (*o*), *meta* (*m*) or *para* (*p*) substituents calculated by a DFT method B3LYP/6-311++G(2d,2p)//B3LYP/6-311G(d,p). Comparison with theoretical data found in literature.

Entry	Substituent	Position	BDE (kcal mol^{-1})	ΔBDE (kcal mol^{-1})	Literature ΔBDE (kcal mol^{-1})
1	—H	–	82.2	–	–
2	—CH_3	*o*	80.2	−2.0	−2.15[a], −1.9[b]
3	—CH_3	*m*	82.2	0	−0.48[a], −0.4[b], −0.4[d]
4	—CH_3	*p*	80.1	−2.1	−2.15[a], −2.1[b], −2.0[c], −2.5[d]
5	—C_2H_5	*o*	80.1	−2.1	nd
6	—$C(CH_3)_3$	*o*	79.3	−2.9	−3.2[d]
7	—CH_2—CH=CH_2	*o*	80.2	−2.0	nd
8	—CH=CH—CH_3	*o*	79.2	−3.0	nd
9	—CH=CH—CH_3	*m*	83.5	+1.3	nd
10	—CH=CH—CH_3	*p*	77.3	−4.9	nd
11	—OCH_3	*o*	80.4	−1.8	−1.4[d]
12	—OCH_3	*m*	83.1	+0.9	−1.2[a], −1.2[b], −1.2[d]
13	—OCH_3	*p*	77.6	−4.6	−5.74[a], −5.9[b], −5.8[c], −6.1[d]

nd: Not determined.
[a] From Klein and Lukes (2006).
[b] From Chandra and Uchimaru (2002).
[c] From Lucarini, Mugnaini, Pedulli, and Guerra (2003).
[d] From Wright et al. (2001).

Table 2
Calculated bond dissociation enthalpies (BDE) of ArO–H in toluene and ΔBDE compared to the phenol value (82.2 kcal mol^{-1}), comparison with theoretical and experimental data found in literature, rate constants *k* of hydrogen transfer from ArOH to DPPH· in toluene at 20 °C, stoichiometric numbers of H atoms σ_{exp} determined with an excess of DPPH· in toluene at 20 °C and mechanisms σ_{theo} involved during the abstraction of H atoms from ArOH by DPPH·.

Phenols	BDE	ΔBDE	ΔBDE (kcal mol^{-1})	*k* (M^{-1} s^{-1})		σ_{exp}	Tentative mechanisms (σ_{theo})					
	(kcal mol^{-1})		Literature	SOK[a]	FOK[b]		α (2H·)	β (2H·)	γ (2H·)	δ (3H·)	ε (1H·)	φ (1H·)
1	80.4	−1.8	−2.1[c], −2.15[d] −2.1[e], −2.0[f], −2.5[g]	–	0.5	1.6		x		x		
1P	76.5	−5.7	nd	–	6.3	1.6		x		x		x
1PP	72.8	−9.4	nd	–	53.9	0.8		x				
2	78.1	−4.1	nd	3.1	2.7	2.5		x		x		
2P	73.3	−8.9	nd	4.0	–	0.8		x				x
3	73.0	−9.2	−7.2[c], −8.9[d]	135	–	2.1			x			
3P	69.5	−12.7	nd	218	–	0.8						x
4	80.4	−1.8	−2.5[c], −3.34[h]	–	0.5	1.6						
4P	77.3	−4.9	nd	–	3.1	1.5						x
5	78.4	−3.8	−4.4[c]	5.7	5.5	2.2		x		x		
5P	75.7	−6.5	nd	39.1	–	1.1		x				x
6	75.7	−6.5	−4.09[h]	30.1	–	1.1					x	
6P	73.6	−8.6	nd	246	–	0.5					x	x
7	72.4	−9.8	−7.3[c]	–	0.18	2.1		x				
8	69.1	−13.1	−10.1[c], −11.3[d]	2570	–	2.0	x					

nd: Not determined
[a] SOK: second order kinetics ($[DPPH]_0 = [ArOH]_0$).
[b] FOK: pseudo-first order kinetics ($[ArOH]_0 \gg [DPPH^{\cdot}]_0$).
[c] Experimental data from radical equilibrium electron paramagnetic resonance REqEPR method (Lucarini & Pedulli, 2010).
[d] From Klein and Lukes (2006).
[e] From Chandra and Uchimaru (2002).
[f] From Lucarini et al. (2003).
[g] From Wright et al. (2001).
[h] From Murakami et al. (2007).

the fragrant phenols *p*-cresol **1**, guaiacol **4**, creosol **5** and isoeugenol **6**. The synthetic phenol BHA **3** was also selected to compare the possible beneficial effect of the substitution on a synthetic antioxidant with an available *ortho*-position. Finally, 2-*tert*-butyl-4-methylphenol **2**, a synthetic phenol, was also retained because its chemical structure is close to those of BHA **3** and creosol **5** (Fig. 1).

The synthesis of the *ortho*-propenyl phenols **1P–6P** starting from phenols **1–6** respectively has been adapted from the method described by De Kimpe and Srikrishna (Fletcher & Tarbell, 1943; Nguyen Van, Debenedetti, & De Kimpe, 2003; Srikrishna & Satyanarayana, 2006). It consists of three steps. The *o*-alkylation of the phenols **1–6** was accomplished by treatment with an alkyl bromide in refluxing acetone giving the ether **A**. A Claisen rearrangement of **A** gives the *ortho*-allylphenol **B** which is further isomerised with potassium *tert*-butoxide at room temperature. This protocol does not work for all phenols and gives yields lower than 2% for the second step. Therefore, for the second and third steps, we resorted to microwave activation in the presence of potassium hydroxide in methanol as outlined in Eq. (6). This route provides better yields and shorter reaction times (see section 2.3).

3.2. Kinetics of hydrogen transfer from phenols to DPPH radical

The antioxidant activity of phenols is generally predicted by calculating the BDE values of the ArO—H bond and assessed by measuring the rate constant for H-atom transfer from the phenol to the peroxyl radical (Litwinienko & Ingold, 2007). Indeed, the logarithm of the rate constant of hydrogen transfer from a phenol to a radical is correlated to the BDE in non-polar non-protic solvents such as aliphatic and aromatic hydrocarbons as it is a radical pathway, the so-called HAT mechanism (Foti, Daquino, Mackie, DiLabio, & Ingold, 2008). Furthermore, it has been shown that there is a strong correlation between the rate constant of hydrogen transfer from

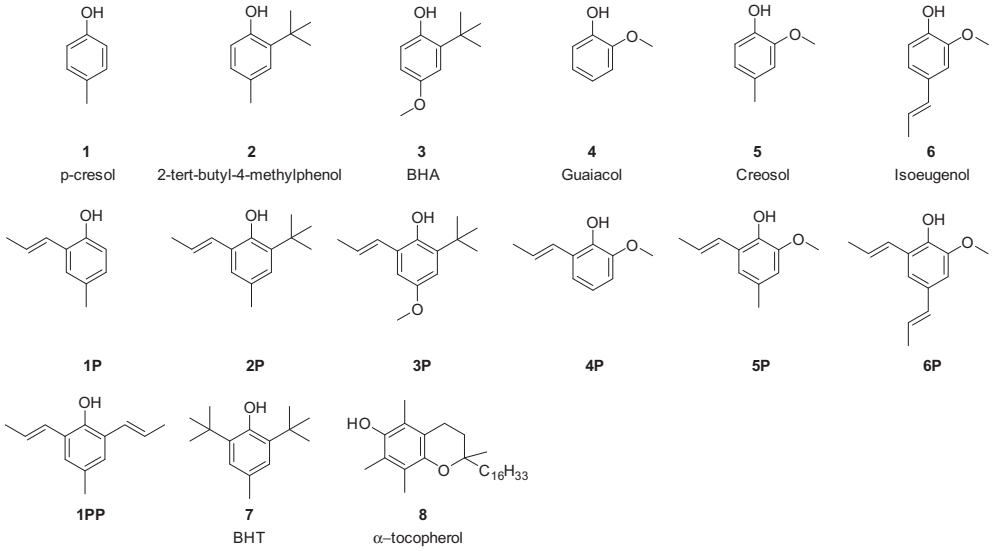
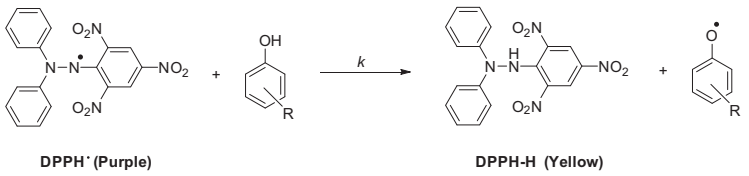


Fig. 1. Chemical structures of the starting phenols (**1**–**6**, **1P**) and their corresponding derivatives bearing a propenyl group in the *ortho* position (**1P**–**6P**, **1PP**). BHT **7** and α-tocopherol **8** are used as references.

phenols to peroxyl (ROO·) and to DPPH· radicals (Foti et al., 2002; Litwinienko & Ingold, 2007). As the DPPH· test is a simple and relevant method, the radical-scavenging capacity of phenols has been evaluated by determining the rate constants k of hydrogen transfer for all phenols **1**–**6** and **1P**–**6P** with DPPH· in toluene (Eq. (7)).



(7)

Two different methods were used to measure k, depending on the reactivity of phenols. For the highly reactive phenols **2**, **3**, **6**, **8** and their propenylated derivatives, equal molar amounts of phenols and DPPH· were allowed to react in toluene. Under these conditions, the second order kinetics can be described by Eqs. (8)–(10).

$$\frac{d[\mathrm{DPPH}^{\cdot}]}{dt} = -k[\mathrm{DPPH}^{\cdot}][\mathrm{ArOH}] \tag{8}$$

$$\frac{d[\mathrm{DPPH}^{\cdot}]}{dt} = -k[\mathrm{DPPH}^{\cdot}]^2 \tag{9}$$

$$\frac{1}{[\mathrm{DPPH}^{\cdot}]} - \frac{1}{[\mathrm{DPPH}^{\cdot}]_0} = kt \tag{10}$$

$$[\mathrm{DPPH}^{\cdot}] = [\mathrm{DPPH}^{\cdot}]_0 \exp\{-k[\mathrm{ArOH}]_0 t\} \tag{11}$$

$$\frac{1}{A - A_f} = \frac{1}{A_0 - A_f} - \frac{k}{\varepsilon - \varepsilon'} t \tag{12}$$

$$Ln\,\frac{A - A_f}{A_0 - A_f} = -k[\mathrm{ArOH}]_0 t \tag{13}$$

$$\sigma_{exp} = \frac{[\mathrm{DPPH}^{\cdot}]_0 - [DPPH^{\cdot}]_f}{[\mathrm{ArOH}]_0} = \frac{A_0 - A_f}{(\varepsilon - \varepsilon')[\mathrm{ArOH}]_0} \tag{14}$$

where A_0, A_f are the DPPH· absorbance at t_0 and t_f respectively, ε its molar absorption coefficient at 517 nm, ε' is molar absorption coefficient of DPPH-H at 517 nm and $[\mathrm{ArOH}]_0$ the initial phenol concentration.

For less reactive phenols **1**, **4**, **5**, **7** and derivatives, k was determined in the presence of excess amounts of phenols to increase the rate of reaction. In this case, $[\mathrm{ArOH}] \approx [\mathrm{ArOH}]_0$ and the pseudo-first order kinetics is described by Eq. (11).

At 517 nm, DPPH· and DPPH-H exhibit a strong (ε) and a weak (ε') molar absorption coefficient respectively which allow monitoring the disappearance of DPPH· (Eq. (7)). Eqs. (10) and (11) can be expressed in terms of absorbance A, A_0 and A_f giving Eqs. (12) and (13) which provide the rate constants k and $k[\mathrm{ArOH}]_0$ as the slopes of the linearised curves obtained by plotting $1/(A - A_f)$ and $\ln (A - A_f)/(A_0 - A_f)$, respectively, *versus* time. In the latter case, the experiment was performed with various concentrations of ArOH to determine k.

2-*tert*-butyl-4-methylphenol **2** with an intermediate reactivity was studied with both methods to check their consistency. Fig. 2 shows the curves obtained with the second method (large excess of **2**). The results obtained with the first method (equal concentration of **2** and DPPH·) are displayed in Fig. S1 (see Supporting information). The rate constant k for phenol **2** was found to be 2.7 $M^{-1}\,s^{-1}$ and 3.1 $M^{-1}\,s^{-1}$ using the first and second methods

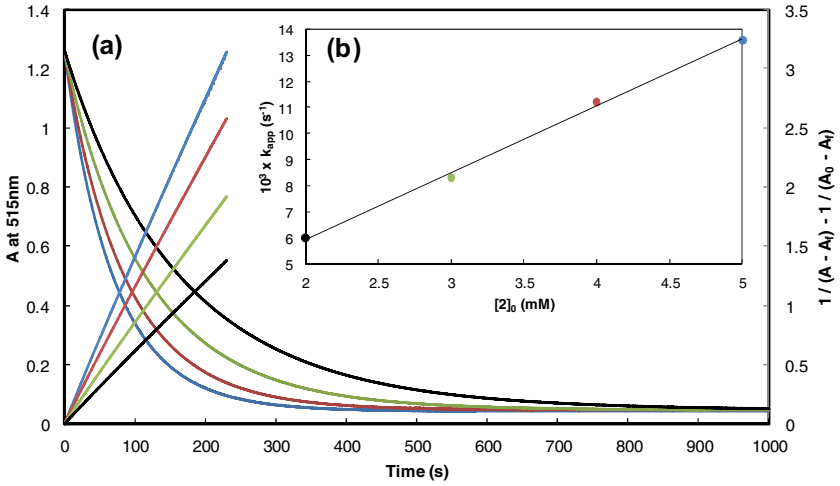


Fig. 2. (a) Evolution of the absorbance of DPPH· in the presence of an excess of 2-*tert*-butyl-4-methylphenol **2** (5 mM (blue), 4 mM (red), 3 mM (green), 2 mM (black)) in toluene and linearised curves according to pseudo-first order kinetics, (b) variation of the apparent rate constant $k[ArOH]_0$ as a function of initial concentrations of **2**. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

respectively. Rate constants obtained for all phenols are summarised in Table 2.

When considering the kinetic analysis of the reaction between DPPH· and ArOH, it is assumed that during the first minutes, only the reaction of DPPH· with the phenolic hydrogen occurs (Eq. (7)). During this period, the curves corresponding to the DPPH· consumption are well fitted by second order (SOK) or pseudo-first order (FOK) kinetics. The logarithm of the rate constants k is fairly well correlated with the calculated BDE values ($r^2 = 0.95$) for phenols **1**–**8** (black dots), provided that the sterically hindered phenol **7** (white dot) is discarded (Fig. 3).

ortho-Propenylated derivatives **1P**–**6P** are more reactive than the parent phenols **1**–**6** towards DPPH· in agreement with the decrease of the BDE values (Table 2). This is also the case when comparing phenols **1PP** to **1P**. However, we can notice significant differences when comparing the effect of the *o*-propenyl group on log$k$ (see Fig. 4), due to steric hindrance of bulky substituents and intra-molecular hydrogen bond between phenolic hydrogen and *o*-methoxy group.

Actually, grafting one or two propenyl groups on non-*ortho*-substituted *p*-cresol **1** (red line) and on *o*-methoxy phenols **1**, **1P**, **4**, **5** and **6** (blue lines) leads to an increase of the reactivity with the radical DPPH· which follows the tendency given by the phenols **1**–**6** and **8** (black line). In contrast, the addition of a propenyl group on the *tert*-butyl phenols **2** and **3** (green lines) has only a moderate accelerating effect because the combined hindrance effects of the *ortho*-*tert*-butyl and propenyl groups dominate over the electronic effect of propenyl group and make the phenolic hydrogen less accessible.

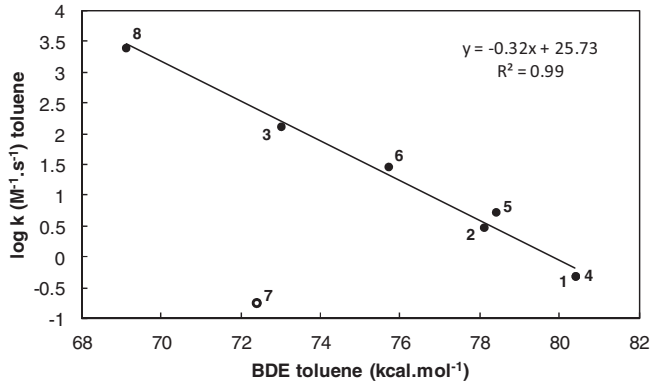


Fig. 3. Plots of the logarithm of the rate constants (log$k$) for the reaction between DPPH· and phenols **1**–**8** (○ sterically hindered phenol BHT **7**, ● other phenols) in toluene at 25.0 °C as a function of the calculated BDE of the ArO–H bond in toluene.

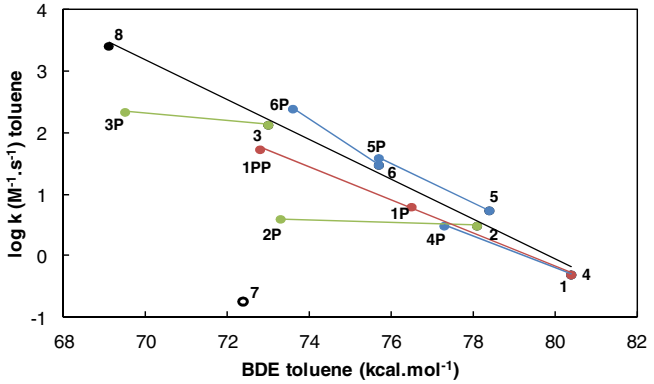


Fig. 4. Comparison of the logarithm of the rate constants (log$k$) for the reaction between DPPH· and phenols **1**–**8** (black line) and propenylated derivatives **1P**–**6P** and **1PP** (blue, green and red lines) in toluene as a function of the calculated BDE of the ArO–H bond in toluene. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

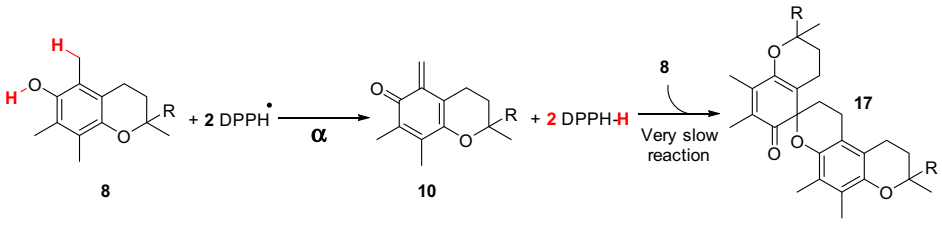
3.3. Stoichiometric number (σ) of phenols ***A*** and ***D***

The stoichiometric number σ of an antioxidant is defined as the maximum number of radicals trapped by one antioxidant molecule. It is determined with the DPPH· test by using the final absorbance reached by DPPH· in the presence of a large excess of DPPH· with respect to the antioxidant (Eq. (14)) (Goupy et al., 2003).

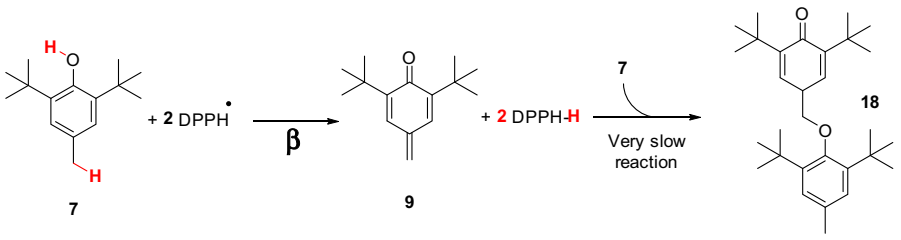
All the stoichiometric numbers σ_{exp} determined for the different phenols (see Table S2 in the Supporting information) are summarised in Table 2. They range from 0.5 for **6P** to 2.5 for **2**, depending on the nature of the substituents at the *ortho* and *para* positions for the phenol group. The determination of the stoichiometric number σ can help in giving an idea of the major reaction pathway but, usually, several competitive pathways are simultaneously involved making the interpretation not straightforward (Bondet, Brand-Williams, & Berset, 1997). The first step of the interaction between an antioxidant and a radical (ROO· or DPPH·) is always the abstraction of the phenolic hydrogen. Then, the obtained phenoxyl radical ArO· may, in turn, transfer a second

hydrogen or dimerise. Such reactions (Eqs. (15)–(19)) have already been reported in the literature by several authors who analysed the products formed during the oxidation of common antioxidants. Analysis of oxidation products is beyond the scope of the present work. Nevertheless, attempts to rationalise our results are entirely based on data collected from the literature.

α-Tocopherol **8** and BHT **7** are known to transfer a second hydrogen from the *p*- or *o*-methyl group leading to a *p*- or *o*-quinone-methide derivative, consistent with a stoichiometric number σ of 2 (Eqs. (15) and (16)) (Wright, Carpenter, McKay, & Ingold, 1997). These *p*- and *o*-quinone-methide derivatives **9** and **10** are electrophilic compounds capable of reacting with the start-



(15)



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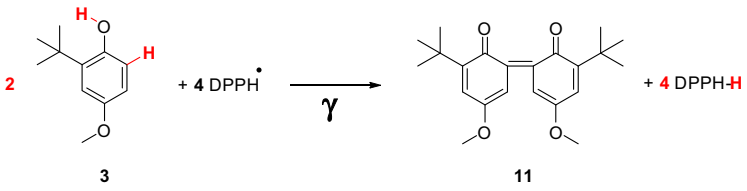

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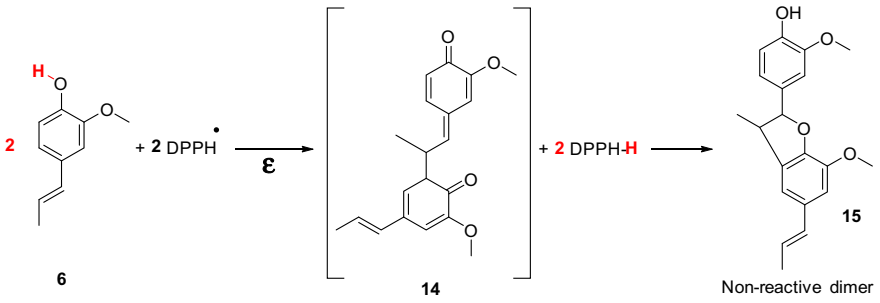

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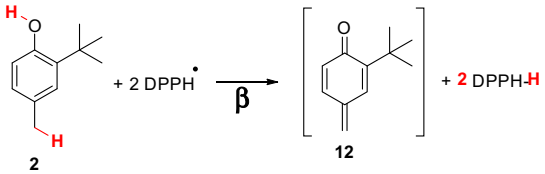
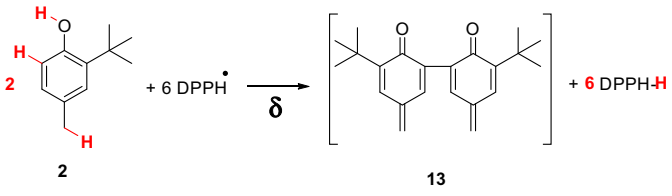
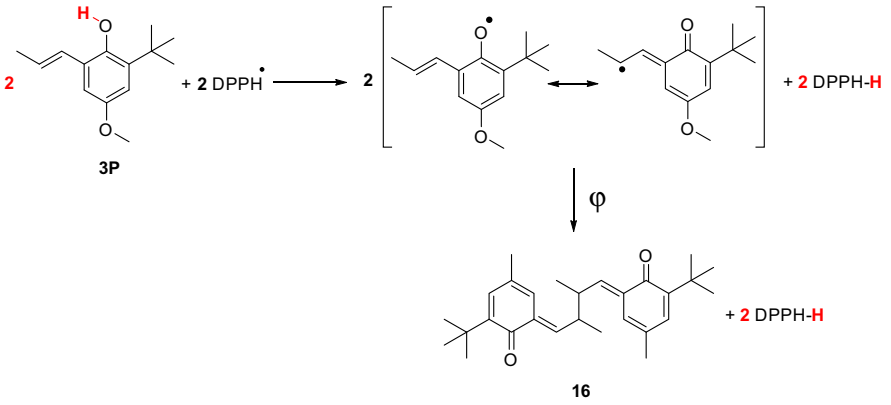


(19a)



(19b)



(20)

ing phenols **7** and **8** to form the dimers **17** and **18** (Boehmdorfer, Patel, Netscher, Gille, & Rosenau, 2011; Bolon, 1970; Bowry & Ingold, 1995). Nevertheless, quinone-methides **10** and **9** react very slowly with α-tocopherol **8** and BHT **7**, respectively. Therefore, under our experimental conditions, dimerisation does not take place and compounds **17** and **18** are not obtained. BHA **3**, which has no methyl substituent, preferentially dimerises at the *ortho*–*ortho* positions, giving a diphenol with antioxidant activity which may transfer two hydrogen atoms (Eq. (17)) (Kadoma, Ito, Yokoe, & Fujisawa, 2008; Omura, 1995). The radical-scavenging capacity of isoeugenol **6** is totally different from that of the other phenols, since it only traps one radical per molecule ($\sigma = 1$). Indeed, its phenoxyl radical dimerises giving dehydrodiisoeugenol **15** (Eq. (18)), the antioxidant activity of which, evaluated by the DPPH· test, was reported to be very weak and practically negligible, compared to that of isoeugenol (Bortolomeazzi, Verardo, Liessi, & Callea, 2010). The formation of a non-reactive dimer implies a stoichiometric number of 1. Another possible explanation is that the aryloxyl radical adds onto a second phenol molecule to form a redox-inert dimeric product.

As far as the *o*-propenyl-phenols **2P**, **3P**, **5P**, **6P** and **1PP** are concerned, their stoichiometric numbers are lower than those of the starting phenols **2**, **3**, **5**, **6** and **1P** (Table 2). On the contrary, phenols **1P** and **4P** with a free *ortho* or *para* position exhibit the same stoichiometric number as the parent phenols **1** and **4**. In the case of **3P** and **5P**, stoichiometric numbers σ are about half that of phenols **3** and **5**, *i.e.* they trap only one radical per antioxidant molecule although they are much more reactive with DPPH·. As proposed previously, dimerisation at the *ortho* position according to Eq. (17) cannot take place. Instead, phenoxyl radicals can be delocalised on the propenyl substituent and may react by a coupling reaction giving the dimer **16** without significant antioxidant activity like dehydrodiisoeugenol (Eq. (20)) (Bortolomeazzi et al., 2010). In this case, the stoichiometric number would be reduced to ≈1. Another explanation could be the formation of dimers with C—O linkages when the two *ortho*-positions on phenolic cycle are occupied (Bolon, 1970). The proposed coupling reaction is based on the oxidation products of isoeugenol **6** identified by Bortolomeazzi et al. (2010). For phenol **2P**, the stoichiometric number decrease is higher than for the others because the dimer of **2** is supposed to reduce 2 or 4 radicals per molecule.

For *p*-cresol **1** and guaiacol **4**, stoichiometric numbers are lower than 2. Ordoudi et al. have studied the reactivity of guaiacol derivatives with DPPH· in ethanol and obtained stoichiometric numbers from 0.6 to 1.5 (Ordoudi, Tsimidou, Vafiadis, & Bakalbassis, 2006). However, guaiacol can provide a coloured dimeric product, i.e. a quinone which can alter the absorbance determination (Montellano, 2010). These results suggest that either coloured products are formed or corresponding dimers are not as reactive as the BHA dimer. Phenol **2** is the most effective compound to inhibit radicals since it can scavenge 2.5 radicals per molecule. In the case of this specific phenol, we propose a competition between 2 pathways. The first one is based on the BHT mechanism β (stoichionetry of 2), whereas the second one results from an *ortho*-dimerisation (stoichiometry of 3) (Kaeding, 1963) as depicted in Eqs. (19a) and (19b) respectively. The different mechanisms likely to take place during hydrogen transfers for all the investigated phenols are summarised in Table 2.

4. Conclusions

The protection against flavour and fragrance oxidation is essential to maintain their sensorial properties during storage. Synthetic or natural antioxidants, such as α-tocopherol, BHT and BHA are the most frequently used antioxidants but the synthetic ones are or will be prohibited because of their suspected toxicity and natural ones are more expensive. For instance, it is known that the toxicity of BHT is linked to its tendency to form quinone methides that form covalent linkages to biological molecules. Sometimes, some phenolic compounds naturally occurring in natural oils can exhibit antioxidant properties, allowing a reduction of the antioxidant quantity in a formulation (*e.g.* isoeugenol in ylang-ylang oil). The BDE calculations predict that the introduction of a propenyl group at the *ortho*-position should enhance the antioxidant properties of this kind of phenolic compound. The kinetics study of the DPPH· reaction with initial and synthetic phenols allowed confirmation that this group does increase the hydrogen transfer capacity of phenols. However, complementary experiments to determine the stoichiometric number by the DPPH· test showed that fewer radicals can be inhibited by the substituted phenols because of the inhibition of the dimerisation reaction of the phenoxyl radicals. The DPPH test highlighted two opposite effects in the antioxidant activity of an *ortho*-substitution of a propenyl group on the phenolic ring. Indeed, this substituent dramatically increases the rate of the first hydrogen transfer from phenol group making it more reactive but reduces the number of hydrogen atoms available per phenol molecule.

The antioxidant property of phenols depends on the BDE values and indirectly on the hydrogen transfer capacity and vice versa but also on the initial structure of the phenol. Indeed, if the introduction of suitable substituents effectively increases the kinetics of the hydrogen transfer reaction during oxidation, it disrupts or inhibits some coupling reactions between phenolic radicals that lead to oxidation products which are themselves antioxidants.

Consequently, the number of radicals trapped by each antioxidant molecule is thereby reduced. The effect on the antioxidant properties induced by propenyl substitution is significant when the phenolic ring can transfer easily a second hydrogen atom or be coupled at the *para*-position. Even if this grafting leads to opposite effects, the results show that the development of new antioxidants with dual properties, *i.e.* antioxidant activity coupled with flavouring or odorous properties, is possible but requires an intimate knowledge of all the mechanisms.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.foodchem.2015.09.007.

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