Food Chemistry 196 (2016) 418–427

Contents lists available at ScienceDirect

Food Chemistry

journal homepage: www.elsevier.com/locate/foodchem

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

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ARTICLE INFO

Article history:
Received 13 April 2015
Received in revised form 5 August 2015
Accepted 4 September 2015
Available online 9 September 2015

Keywords:
Phenol
Antioxidant
Autoxidation
BDE
DPPH radical
ortho-Propenyl group

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.

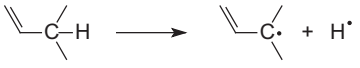
1. Introduction

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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http://dx.doi.org/10.1016/j.foodchem.2015.09.007
0308-8146/

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.