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Short communication

Dihydroperoxidation facilitates the conversion of lipids to aldehydic products *via* alkoxyl radicals

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ABSTRACT

The mechanisms of formation of many aldehydic lipid oxidation products remain unclear, and the involvement of peroxyl radical additions in some cases was recently suggested. Here, the effect of α-tocopherol, a peroxyl radical trap, on the formation of aldehydic phospholipids from a phosphatidylcholine hydroperoxide was studied by electrospray ionization mass spectroscopy (ESI-MS). Based on the observed differential enhancement or suppression of formation of different aldehydes, new pathways are deduced for aldehyde formation *via* alkoxyl radicals derived from dihydroperoxy derivatives.

Lipid oxidation in foods or *in vivo* results in the formation of a variety of aldehydic products which are implicated in the development of physiological disorders such as atherosclerosis, diabetes, and cancer (Kuksis, 2000). Knowledge of the mechanisms of formation of these aldehydes is therefore important for effective prevention of these disorders. Although some aldehydes are formed by the classical β-scission of alkoxyl radicals, mechanisms of formation of some major aldehydes remain unclear. The β-scission of alkoxyl radicals, which simultaneously produces an aldehyde and a carbon-centred radical, is facile if the carbon-centred radical is allylic but not if it is alkyl (Onyango et al., 2001). Thus, decomposition of a phosphatidylcholine (PC) bearing the 9-hydroperoxide of linoleic acid at the *sn*-2-position (PC-9-LA-OOH **1** in Scheme 1) *via* alkoxyl radical **a** may produce only a small amount of 2,4-decadienal and alkyl radical **b**. Also, the cyclization of **a** may sequentially lead, *via* peroxyl radical **c**, epoxyhydroperoxy-PC **2** and alkoxyl radical **d**, to the formation of small amounts of 2-(13′-oxo-9′,10′-epoxy-11′-tridecenoyl)-PC **3** and alkyl radical **e**. However, β-scission of **a** is unlikely to afford 2-(9′-oxononanoyl)-PC **4** and vinyl radical **f**, since such vinyl radical formation is highly energetically unfavorable (Gardner & Plattner, 1984). Nevertheless, 9-oxononanoic acid or its esters such as **4** are the predominant non-volatile aldehydes formed from linoleic acid or its esters, respectively (Gardner & Plattner, 1984; Kuksis, 2000). Such compounds were therefore suggested to be formed heterolytically by the acid-catalyzed Hock cleavage of hydroperoxides (Gardner & Plattner, 1984). Other important compounds that were postulated to be formed by Hock cleavage are 4-hydroperoxy-2-nonenal and 12-oxo-9-hydroperoxy-10-dodecenoic acid (Schneider, Tallman, Porter, & Brash, 2001). Compound **5** is a PC ester of the latter, and its 9′-keto or hydroxyl derivatives **6** and **7** are proatherogenic (Podrez et al., 2002). However, it was recently shown that autoxidation conditions are not acidic enough to allow Hock cleavage (Schneider et al., 2005). Thus, alternative pathways for the formation of compounds such as **4**–**7** *via* intermolecular or intramolecular addition of peroxyl radicals have been postulated (Onyango & Baba, 2009; Schneider, Porter, & Brash, 2008).

At high concentrations, α-tocopherol inhibits reactions of fatty acid hydroperoxides *via* peroxyl radicals but does not prevent their conversion to hydroxy- or ketodiene derivatives *via* alkoxyl radicals (Makinen & Hopia, 2000). By extension, we considered that under such conditions, there should be (i) negligible conversion of PC-LA-OOH **1** to aldehydes **4**–**7** if they are exclusively formed *via* peroxyl radical addition and (ii) enhanced relative importance of aldehydes formed *via* alkoxyl radicals, such as **3**. Moreover, addition of Fe^{2+} to such a system should highly favor alkoxyl radical reactions because Fe^{2+} promotes alkoxyl radical formation and α-tocopherol reduces Fe^{3+} formed in the system back to Fe^{2+} (Yamamoto & Niki, 1988). Thus, we synthesized PC-LA-OOH **1** and subjected it to Fe^{2+}-mediated decomposition at 37 °C in the presence or absence of α-tocopherol. Aliquots of the reaction mixtures were taken at different times and analyzed by ESI-MS, which has been used in similar studies (Onyango et al., 2001, Onyango,

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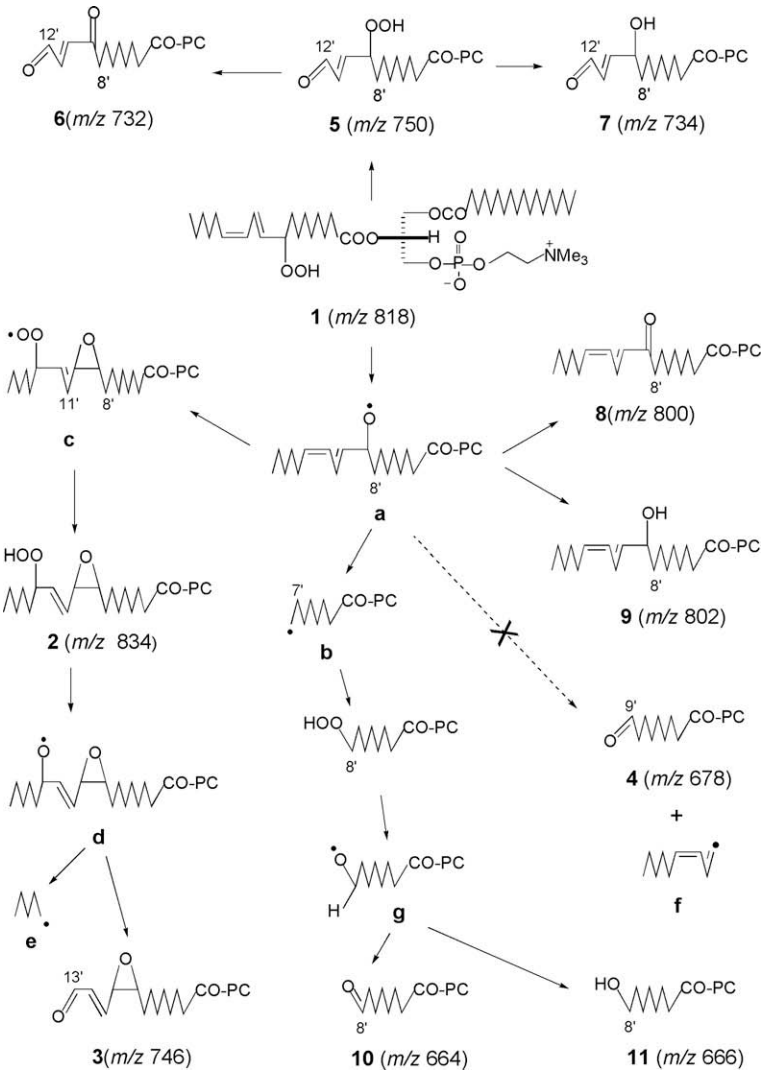

Scheme 1. Decomposition products of PC-9-LA-OOH **1** showing their expected *m/z*s in ESI-MS spectra such as Fig. 1.

Nakajima, Kaneko, Matsuo, & Baba, 2004). The ESI-MS spectrum of undecomposed PC-LA-OOH **1** consisted of only one peak at *m/z* 818. Representative spectra obtained after some decomposition occured in the absence or presence of α-tocopherol are shown in Fig. 1. Spectra taken at different times had different product profiles (Compare 1A and B). There were peaks corresponding to all the known compounds **1**–**11**, which are shown with their expected *m/z*s in Scheme 1. Carbonyl groups in aldehydic products were confirmed by derivatization with methoxylamine hydrochloride (Onyango et al., 2004). Aldehydic lipids are readily oxidized to the corresponding acids (Lehtinen, Nevalainen, & Brunow, 2000; Onyango et al., 2004). This involves conversion of an aldehyde to a peracid derivative whose Baeyer–Villiger reaction with another aldehyde molecule gives two molecules of acid (Lehtinen et al., 2000). Peaks corresponding to acids derived from aldehydes **4**–**7** are found at *m/z*s 694, 766, 748, and 750, respectively (Fig. 1B). The detection of PC peracids has not been reported. However, peaks at *m/z*s 710, 782, 764, and 766 (Fig. 1B) are consistent with such derivatives of **4**–**7**, respectively.

During analysis of phospholipids or phospholipid oxidation products by ESI-MS, the relative intensities of the protonated molecular ion peaks increases with increasing product concentration (DeLong et al., 2001; Onyango et al., 2001). Thus, by comparing peak heights of aldehydes **3**–**7** with that for ketodiene-PC **8** in Fig. 1B andC, it is evident that, as predicted (*vide supra*), α-tocopherol enhanced the formation of epoxyaldehyde PC **3** but suppressed aldehyde-PCs **4**–**7**. This confirms the formation of **4**–**7** *via* peroxyl radical reactions without ruling out some alkoxyl radical-dependent pathways (especially for aldehyde-PC **4** whose peak is more prominent than that for **3** in both Fig. 1B and C).

The formation of 2-(8′-oxooctanoyl)-PC **10** should at least partly occur by oxidation of radical **b** according to Scheme 1. Here, the conversion of alkoxyl radical **g** to aldehyde-PC **10** with the loss of a hydrogen atom should be facile, being analogous to the conversion of alkoxyl radical **a** to ketodiene-PC **8**. The enhancement of formation of 2-(8′-hydroxyoctanoyl)-PC **11** relative to **10** by α-tocopherol (Compare Fig. 1B and C) confirms the involvement of alkoxyl radical **g**. Decarboxylation of the peracid intermediate involved in the conversion of aldehyde-PC **4** to 2-(9′-carboxy-nonanoyl)-PC (*m/z* 694) should also afford alkyl radical **b**, since such decarboxylation accompanies the predominant Baeyer–Villiger oxidation (Lehtinen et al., 2000). Hence, suppression of formation of **4** by α-tocopherol (*vide supra*) should result in suppression of formation of **10** by the latter mechanism. However, this does not rationalize the greater formation of **3** than **10** in the presence of α-tocopherol (Fig. 1C) because conversion of alkoxyl radical **d** to