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Grafting of α-tocopherol upon γ-irradiation in UHMWPE probed by model hydrocarbons

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ABSTRACT

Today, UHMWPE implants are stabilized with α-tocopherol and cross-linked by irradiation in order to reduce wear. Little is known about the structural transformation of the antioxidant α-tocopherol upon irradiation. In the present investigation, the major irradiation reaction products of α-tocopherol dissolved at 0.1 wt.% in liquid model hydrocarbons were characterized spectroscopically and by independent synthesis. We observed only a single product group, namely phenolic alkyl ethers formed by radical recombination of a phenoxyl radical with a secondary alkyl radical. The irradiation dose is the parameter which controls the amount of consumption of α-tocopherol. At a dose of 27.5 kGy, 31–34% of α-tocopherol was transformed into the corresponding ether, while at 97.9 kGy, the degree of transformation was 68–76%. The observed ether formation in the liquid model hydrocarbons explains two significant observations for the α-tocopherol stabilized polymers, namely depletion of the α-tocopherol's phenol group upon irradiation and "grafting", i.e. formation of a chemical bond between the polymer and its antioxidant.

1. Introduction

The use of α-tocopherol in food packaging made of polyethylene goes back to the 1980s [1]. Nowadays, stabilisation by this antioxidant is used in many PE foils used for food contact. Concentrations of α-tocopherol for such applications are in the range of 100–300 ppm, including pouches intended for γ sterilisation [2,3]. Around the year 2000, α-tocopherol was postulated as antioxidant to be used in UHMWPE for orthopaedic implants [4] and extensive investigations initiated on the mechanical, physical, chemical and wear behaviour of such stabilised UHMWPE. For reviews refer to Refs. [5–7]. Today, an ASTM standard specification for medical grade UHMPE blended with vitamin E is published [8] and blends of UHMWPE powder with 0.1% α-tocopherol are available commercially [9]. Often, UHMWPE used as articulation material in joint replacement is cross-linked by irradiation in order to reduce wear. Although it was shown that after γ-irradiation to a dose as high as 100 kGy, UHMWPE blended with 500 ppm α-tocopherol is still protected against oxidative degradation [10–12], little is known about the reactions and the disposition of α-tocopherol in the polymer after high energy irradiation. In the experiments of Mallégol et al. [2], HDPE was irradiated step by step and the polymer was analysed immediately after each irradiation by FTIR. An exhaustion of the phenolic function of α-tocopherol with increasing irradiation dose was observed i.e., the irradiation dose is the parameter which controls the amount of consumption of α-tocopherol in the polymer. As postulated before by Al-Malaika et al. [13] it is concluded that the α-tocopherol molecule is grafted to the polymer back chain. Mallégol and coworkers report a "grafted quinone" and suggest that the α-tocopherol is grafted to the macromolecule by a peroxide bond on the site of the former phenol group [2].

However, the determination of the particularities of chemical bonds by FTIR in a solid body is difficult. Liquid sample compounds with the same or similar characteristics may be used to elucidate the details of chemical bonds. Liquids may be analysed by a wide palette of analytical techniques including (but not limited to): HPLC, GC–MS, NMR, MALDI-TOF-MS. Using this approach, Maslovskaya and Savchenko [14] analysed tert-butylated pyrocatechol dissolved in hydrocarbons after γ-irradiation. Compared to α-tocopherol, this catechol has two (instead of one) reactive –OH sites on the benzene ring. Employing NMR and GC–MS, the products resulting after irradiation where analysed as monoalkyl ethers originating from the reaction of one catecholic hydroxy group and the hydrocarbons. Analogue to this approach, the current investigation started with 0.1 wt.% solutions of α-tocopherol in two different hydrocarbons which where irradiated and afterwards analysed by different, complementary spectroscopic methods.

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2. Materials and methods

2.1. Chemicals

α-Tocopherol (synthetic, ≥96%), cyclohexane (CHROMASOLV® Plus, ≥99.9%), *n*-octane (puriss. p.a., ≥99.0%), tetrahydrofuran (puriss., ≥99%), toluene (water-free, 99.8%), 1,1′-bicyclohexyl (99%), α-cyano-4-hydroxycinnamic acid (Fluka, CHCA, ≥99%), *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (Aldrich, MSTFA), cyclohexanol (99%), 1-octanol (analytical standard), 2-octanol (≥97%), 3-octanol (≥97%), tetrahydrofuran (puriss., ≥99%), hydrogen peroxide (30% w/w in H_2O), d^1-chloroform (99.96 atom % D), triphenylphosphine (≥95%), spherical silica gel (Fluka, high purity, 60–80 Å pore diameter), sodium sulfate (Fluka, purum, p.a., ≥99%), and diisopropyl azodicarboxylate (Aldrich, 95%) were obtained from Sigma–Aldrich, Buchs, Switzerland. All chemicals were used without further purification unless mentioned otherwise.

2.2. Instrumentation

Characterization by gas chromatography-mass spectrometry (GC–MS) was performed on an Agilent 6890 Series gas chromatograph equipped with an HP-5MS 25 μm column (30 mm × 0.250 mm i.d., Agilent J&W). Temperature program was 200 °C, 5 °C/min until 310 °C, the mobile phase was He at a flow rate of 4 ml/min, and the injection volume was 1 μl. Detection was done with an Agilent 5973 mass detector using electron impact ionization.

Characterization by high performance liquid chromatography (HPLC) was performed on a HP 1100 Series HPLC equipped with an Interchrom Modulo-Cart QS Upitsphere ODB, 5 μm column (125 mm × 4.0 mm i.d.). Detection was done with a DAD at 290 nm. Mobile phase was methanol:acetic acid 100:0.2 (v/v) at a flow rate of 1.5 ml/min. Trimethylsilyl derivatives were prepared by mixing 1 ml of sample with 100 μl MSTFA for 25 min at room temperature [15].

Matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry (MALDI-TOF-MS) spectra were recorded on a Bruker Daltonics Reflex III in a positive ion reflectron mode. Ionization was achieved using a N_2-Laser (337 nm) with 3 ns pulse width at a frequency of 10 Hz. Samples were prepared on a stainless steel plate and CHCA was used as matrix.

Nuclear magnetic resonance (NMR) spectra were recorded at room temperature on a Bruker Advance DPX 300 (300 MHz) spectrometer (Bruker BioSpin AG, Fällanden, Switzerland). Chemical shifts are given in ppm relative to tetramethylsilane as internal standard ($\delta = 0$ ppm). Coupling constants *J* are given in Hertz. All ^{13}C NMR spectra were broad-band decoupled and the multiplicity was evaluated using DEPT experiments (distorsionless enhancement by polarization transfer). The fine structure of signals is specified as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Signals were assigned by means of the 2D-experiments COSY (correlation spectroscopy), HSQC (heteronuclear single quantum coherence) and HMBC (heteronuclear multiple bond coherence).

The ultrasonic bath (TUC-75, M. Scherer AG, Wil SG, Switzerland), which was used for the Mitsunobu reaction, was operated at a frequency of 35 kHz.

2.3. Preparation and characterization of samples

Solutions of 100 ml cyclohexane or *n*-octane containing 0.1 wt.% α-tocopherol were saturated with nitrogen by bubbling N_2 through the solution for 1 h followed by sealing in 100 ml DURAN® premium flasks with PE/PTFE caps under N_2 atmosphere. The samples were then γ-irradiated at a dose of 0.0 kGy (blank), 27.5 kGy, and 97.9 kGy (BBF Sterilisationsservice, Kernen-Rommelshausen, Germany).

The samples were either directly analysed (denoted as crude samples) by GC–MS, GC–MS/MSTFA-derivatisation, and MALDI-TOF-MS, or the solvents cyclohexane or *n*-octane were removed on a rotary evaporator (0.1 mbar, denoted as evaporated samples) prior to GC–MS and HPLC analysis. NMR samples were purified by flash chromatography (silica gel, toluene) after evaporating the solvent in order to remove dimeric reaction products between the solvents themselves.

2.4. Preparation of 6-O-α-tocopherol ethers as reference material

The synthesis of 6-*O*-α-tocopherol ethers followed the general procedure given by Lepore and He. [16].

6-O-cyclohexyl-α-tocopherol ether **1**: 0.624 g of α-tocopherol 1 (1.45 mmol, 1.00 eq), 0.152 g of cyclohexanol (1.52 mmol, 1.05 eq) and 0.399 g of triphenylphosphine (1.52 mmol, 1.05 eq) were added into a 10 ml round bottom flask and dissolved in 3 ml tetrahydrofuran that has been dried by molecular sieve. The reaction mixture was then treated with ultrasound until everything had been dissolved. Then, 0.31 ml of diisopropyl azodicarboxylate (1.52 mmol, 1.05 eq) were added dropwise within 2 min upon ultrasonication and the ultrasonication was continued for another 15 min. The reaction mixture was concentrated in a rotary evaporator. The residue was dissolved in 20 ml of cyclohexane and solvent extracted with aqueous hydrogen peroxide, until the remaining triphenylphosphine had been reacted. The organic phase was dried with sodium sulfate, filtered and concentrated on a rotary evaporator. The residue (yield 20%) was purified by column chromatography (silica gel, 100% toluene) and 6-O-cyclohexyl-α-tocopherol ether **1** was obtained as yellowish oil (purity according to GC: 95.6%). ^1H NMR ($CDCl_3$): $\delta = 0.82$–0.86 (6H, C(4′a)H_3 & C(8′a)H_3), 0.84–0.89 (6H, 2 × C(13′)H_3), 1.14 (2H, C(11′)H_2), 1.20–1.30 (4H, C(6′)H_2 & C(10′)H_2), 1.22 (s, 3H, C(2a)H_3), 1.26 (8H, C(3′)H_2, C(5′)H_2, C(7′)H_2, C(9′)H_2), 1.35-1.55 (2H, C(2″)H'H, C(6″)H'H), 1.35-1.40 (2H, C(2′)H_2), 1.41 (1H, C(8′)H), 1.45 (1H, C(4′)H), 1.54 (1H, C(12′)H), 1.55 (2H, C(1′)H_2), 1.55–1.60 (2H, C(4″)H_2), 1.68–1.87 (m, 2H, C(3)H_2), 1.68–1.87 (m, 2H, C(3″)H'H, C(5″)H'H), 1.95-2.05 (m, 2H, C(2″)H′H, C(6″)H′H), 2.08 (s, 3H, C(8a)H_3), 2.11 (s, 3H, C(5a)H_3), 2.15 (s, 3H, C(7a)H_3), 2.56 (t, $J = 6.77$, 2H, C(4)H_2), 3.53 (tt, $J = 3.97, 10.54$, 1H, C(1″)H) ^{13}C NMR ($CDCl_3$): $\delta = 11.88$ (C-8a), 13.03 (C-5a), 13.89 (C-7a), 19.70 (C-4′a, C-8′a), 20.78 (C-4), 21.05 (C-2′), 22.64 (C-13′), 22.73 (C-13′), 23.89 (C-2a), 24.45 (C-6′), 24.83 (C-10′), 24.93 (C-3″, C-5″), 25.78 (C-4″), 28.00 (C-12′), 31.38 (C-3), 32.70 (C-8′), 32.80 (C-4′), 32.93 (C-2″, C-6″), 37.45 (C-3′, C-5′, C-7′, C-9′), 39.40 (C-11′), 40.13 (C-1′), 74.66 (C-2), 81.67 (C-1″), 117.33 (C-4a), 122.59 (C-8), 126.34 (C-5), 128.35 (C-7), 147.15 (C-6), 147.30 (C-8b) GC–MS (M = $C_{35}H_{60}O_2$; *m*/*z* = 512.46; t_r = 21.17 min, (intensity in %)): 165.20 $[C_{10}H_{13}O_2]^+$ (72.2); 205.20 $[C_{13}H_{17}O_2]^\bullet$ (7.6); 247.25 $[C_{16}H_{23}O_2]^+$ (6.4); 430.50 [M − C_6H_{10}] (100.0); 512.60 [M] (6.0); 513.60 [$^{13}C^{12}C_{34}H_{60}O_2$] (2.3); 514.55 [$^{13}C_2^{12}C_{33}H_{60}O_2$] (0.4).

6-O-(1-octyl)-α-tocopherol ether **2a**: Here, 0.072 g of 1-octanol (0.55 mmol, 1.05 eq) were used instead of cyclohexanol and the further chemicals were scaled accordingly. The solvents tetrahydrofuran and cyclohexane were kept at 3 ml and 20 ml respectively. Without purification by column chromatography, 6-O-(1-octyl)-α-tocopherol ether **2a** was obtained as a crude product (yield 88%). GC–MS (M = $C_{37}H_{66}O_2$; *m*/*z* = 542.51; t_r = 22.42 min: 165.20 $[C_{10}H_{13}O_2]^+$ (100.0); 205.20 $[C_{13}H_{17}O_2]^\bullet$ (8.9); 277.30 $[C_{18}H_{29}O_2]^+$ (34.7); 317.30 $[C_{21}H_{33}O_2]^\bullet$ (7.4); 430.50 [M − C_8H_{16}] (15.2); 542.70 [M] (77.3); 543.65 [$^{13}C^{12}C_{36}H_{66}O_2$] (31.6); 544.65 [$^{13}C_2^{12}C_{35}H_{66}O_2$] (6.7).

6-O-(2-octyl)-α-tocopherol ether **2b**: Here, 0.082 g of 2-octanol (0.63 mmol, 1.05 eq) were used instead of cyclohexanol and the