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.

Keywords

vitamin E; mechanism; gamma irradiation; grafting; degradation; 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 to 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 [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 co-workers 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.

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), triphenylphosphin (≥ 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 x 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 (300MHz) spectrometer (Bruker BioSpin AG, Fällanden, Switzerland). Chemical shifts are given in ppm relative to tetramethylsilane as internal standard (δ = 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 one hour 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 (80 °C, 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 cylcohexane 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 %). ^{1}H-NMR ($CDCl_3$): δ = 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 ($CDCl_3$): δ = 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 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-(2-octyl)-α-tocopherol ether **2b** was obtained as a crude product (yield 95 %). GC-MS (M = $C_{37}H_{66}O_2$; m/z = 542.51; t_r = 20.91 min: 165.20 [$C_{10}H_{13}O_2$]$^+$ (74.0); 205.20 [$C_{13}H_{17}O_2$]$^\bullet$ (7.8); 277.30 [$C_{18}H_{29}O_2$]$^+$ (5.1); 317.30 [$C_{21}H_{33}O_2$]$^\bullet$ (1.1); 430.50 [M – C_8H_{16}] (100.0); 542.70 [M] (3.8); 543.70 [$^{13}C^{12}C_{36}H_{66}O_2$] (1.6); 544.70 [$^{13}C_2{}^{12}C_{35}H_{66}O_2$] (0.3).

6-O-(3-octyl)-α-tocopherol ether **2c**: Here, 0.066 g of 2-octanol (0.51 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-(3-octyl)-α-tocopherol ether was **2c** obtained as a crude product (yield 86 %). GC-MS (M = $C_{37}H_{66}O_2$; m/z = 542.51; t_r = 20.21 min: 165.20 [$C_{10}H_{13}O_2$]$^+$ (66.2); 205.20 [$C_{13}H_{17}O_2$]$^\bullet$ (7.2); 277.30 [$C_{18}H_{29}O_2$]$^+$ (3.5); 317.30 [$C_{21}H_{33}O_2$]$^\bullet$ (0.7); 430.50 [M – C_8H_{16}] (100.0); 542.70 [M] (2.2); 543.70 [$^{13}C^{12}C_{36}H_{66}O_2$] (0.9); 544.70 [$^{13}C_2{}^{12}C_{35}H_{66}O_2$]

3. Results

3.1. α-Tocopherol in cyclohexane

The crude γ-irradiated samples where α-tocopherol had been dissolved in cyclohexane were directly analysed by GC-MS and MALDI-TOF-MS. The total ion current (TIC) of the GC chromatogram showed only a few significant peaks, namely the α-tocopherol-peak at 15.92 min and an additional peak at 21.12 min, with a mass peak of m/z = 512, formally the cyclohexene-adduct (Δ m/z = 82 ≡ C_6H_{10}) of α-tocopherol (Figure 1). Early peaks in the GC chromatogram between 1 and 4 minutes show typical cyclohexyl fragments (m/z = 82) in their mass spectra and are possibly the result of γ-irradiation induced intermolecular radical reactions between the solvent molecules. The peak at 1.1 min was shown to be 1,1'-bicyclohexyl by injecting a reference sample. The MALDI-TOF-MS spectrum of the 97.9 kGy γ-irradiated sample showed two weak peaks at m/z = 430 and 512, α-tocopherol and the formal cyclohexene adduct. Similar results were observed by HPLC, where the UV-chromatograms of the γ-irradiated and evaporated samples gave rise to two significant peaks, the α-tocopherol peak at 4.31 min and an additional peak at 19.95 min.

A first indication for the structure of the formal cyclohexene-adduct of α-tocopherol was obtained from the GC-MS spectra after MSTFA treatment, where alcohols are converted into trimethylsilyl ethers: as expected, the phenolic group of α-tocopherol was partially converted into the trimethylsilyl ether, which gave rise to an additional peak at 16.13 min with m/z = 502, next to the α-tocopherol peak. No additional peak was observed for the formal cyclohexene adduct of α-tocopherol at 21.12 min, which indicated the absence of a free phenolic group in the formal cyclohexene adduct. The

simplest structure of a formal cyclohexene adduct of α-tocopherol without free phenolic group would be the corresponding 6-*O*-cyclohexyl-α-tocopherol ether. Reference material for the suspected 6-*O*-cyclohexyl-α-tocopherol ether was synthetically accessible from α-tocopherol and cyclohexanol following the Mitsunobu reaction [17,18]. GC-MS and HPLC analysis of the 6-*O*-cyclohexyl-α-tocopherol ether resulted in peaks at 21.12 min and 19.95 min, respectively, (Figure 1). The mass spectrum of the peak at 21.12 min was also identical with the one obtained from the irradiated products.

^{1}H-NMR spectra of the isolated formal cyclohexene adduct of α-tocopherol from the γ-irradiated sample were identical with ^{1}H-NMR spectra of the synthesized 6-*O*-cyclohexyl-α-tocopherol ether (Figure 2). In both samples, the phenolic hydrogen atom of α-tocopherol, which is expected around 4.17 Hz, is missing, while a new characteristic triplet of a triplet at 3.53 Hz is observed, that was assigned to the C(1'') hydrogen atom of the cyclohexyl ether.

3.2. α-Tocopherol in n-*octane*

The crude γ-irradiated samples where α-tocopherol had been dissolved in *n*-octane were analysed by GC-MS as well (Figure 3). Instead of a single formal cyclohexene adduct, three formal octene adducts (Δ *m*/*z* = 112 ≡ C_8H_{16}) were observed in the chromatogram of the crude sample at 19.79, 20.15 and 20.86 min. Again, these peaks remained unaffected upon derivatization with MSTFA, while the also present α-tocopherol was partially converted into its corresponding trimethylsilyl ether. By preparing reference ethers starting from α-tocopherol and 1-, 2-, or 3-octanol, the peaks at 20.15 and 20.86 min were assigned as 6-O-(3-octyl)-α-tocopherol ether and 6-O-(2-octyl)-α-tocopherol ether, respectively. By exclusion principle, the peak at

19.79 min must be the 6-O-(4-octyl)-α-tocopherol ether, since the 6-O-(1-octyl)-α-tocopherol ether appears at 22.42 min. A small peak at 22.42 min in the irradiated samples indicates the formation of the primary ether **2a**. In the HPLC chromatogram, the three 6-O-(octyl)-α-tocopherol ethers were not resolved, but two peaks at 25.07 and 27.28 min were observed.

3.3. Influence of the applied γ-irradiation dose

In all irradiated samples, ethers between the solvent and α-tocopherol were observed besides the intact α-tocopherol. The degree of ether formation α increased with increasing γ-irradiation dose as given in Table 1 and reached 70 to 80 % for the 97.9 kGy irradiated sample. The integrated TICs from the GC-MS spectra are not quantitative, but the ionization cross section of the different compounds depends mainly on the preserved chromanol backbone. Moreover, the by far most abundant fragments in the mass spectra of α-tocopherol and its 6-*O*-alkyl ethers are identical, namely the “fragment” at *m*/*z* = 430, the $[\alpha\text{-tocopherol}]^{\bullet+}$ ion, and the retro Diels-Alder product $[C_{10}H_{13}O_2]^+$ at *m*/*z* = 165. Determination of the degree of ether formation for the 27.5 kGy irradiated α-tocopherol dissolved in cyclohexane based on ^{1}H-NMR gave α(6-*O*-cyclohexyl-α-tocopherol ether) = 40 %, which is within the same magnitude as the GC-MS data with α = 34 %.

4. Discussion

The γ-irradiation of the model hydrocarbons cyclohexane and *n*-octane which were "stabilized" with 0.1 wt. % of the antioxidant α-tocopherol has clearly induced the formation of significant amounts of 6-*O*-alkyl-α-tocopherol ethers. In case of cyclohexane as solvent, approximately 70 % of α-tocopherol were exclusively transformed into the 6-*O*-cyclohexyl-α-tocopherol after irradiating with 97.9 kGy. The presence of a single reaction product implies a reaction mechanism with thermodynamically favorable radical intermediates. The effect of γ-irradiation on hydrocarbons, in particular polyethylene, has been studied thoroughly and the formation of $R^{\bullet}$ as a starting reactive species derived from radiolysed RH has been widely accepted [19-21]. In case of cyclohexane, C-H cleavage leads to the formation of a hydrogen atom and a cyclohexyl radical (Scheme 1, reaction (1)). The presence of cyclohexyl radicals in our γ-irradiated cyclohexane samples is seen in the formation of 1,1'-bicyclohexyl. Instead of reacting with another cyclohexane, the generated hydrogen atom or cyclohexyl radical can also react with α-tocopherol upon formation of a phenoxy radical, reaction (2) [14,22]. Burton *et al.* investigated the homolytic oxidation of the model compound PMC (2,2,4,7,8-pentamethyl chroman-6-ol) and found an almost exclusive formation of the chromanoxyl radical while they were not able to observe by ESR (electron spin resonance spectroscopy) the formation of the alternative chromanol methide radical [22]. The spin density of the chromanoxyl radical was calculated to be mainly concentrated on the 6-*O*-oxygen and the 8b-*C*-carbon [23]. Radical recombination between the chromanoxyl radical and another cyclohexyl radical, $R"^{\bullet}$, may then result in the observed 6-*O*-cyclohexyl-α-tocopherol ether, reaction (3), [14,24]. Irradiation induced monoetherfication of catechols by hydrocarbons was also reported by Maslovskaya and Svchenko [14].

Alternative reaction pathways that could generate different reaction products such as direct α-tocopheroxyl radical formation by γ-radiation as well as bimolecular self-reactions between two α-tocopheroxyl radicals are less important at the given experimental conditions with only 0.1 wt. % of dissolved α-tocopherol. Interestingly, C(4)-C(4') self-coupling of 2,6-dialkylphenols upon γ-irradiation was reported by Brodilová et al. [24] for concentrated phenol solutions in hydrocarbons (5 to 20 wt. %).

With *n*-octane instead of cyclohexane as the solvent, three major ether products were observed at similar amount. This observation is in line with the three chemically equivalent CH_2-groups in *n*-octane, which allow the formation of three different secondary octyl radicals of similar energy (Scheme 2). Each of those three radicals may then react with the chromanoxyl radical upon formation of the three observed ethers. Primary octyl radicals originating from the chemical equivalent CH_3-groups in contrary are significantly less stable than the secondary radicals and formation of the primary ether does compete with the rapid isomerization to a secondary radical before reacting with the chromanoxyl radical.

The antioxidant effect of α-tocopherol on PE upon γ-irradiation has been studied extensively [2,3,5,7,10-13,25]. Most of those studies concentrated on the formation of oxidation products in PE, radical formation or cross linking. Only a few studies, however, have investigated the chemical transformation or degradation of α-tocopherol. Typically, degradation of α-tocopherol was observed in terms of loss of the IR absorption of the phenolic OH group [2] or by polymer extraction studies [25]. While there is general agreement on the loss of the phenolic OH group upon irradiation, almost nothing is known about the structure of the degradation products

of α-tocopherol. Some studies explicitly mention the formation of chemical bonds between the polymer backbone and α-tocopherol, also denoted as “grafting”, such as Mallègol et al. [2] who mention grafting via a peroxo group or Wolf and Muratoglu who suggest grafting via the α-tocopherol’s aliphatic tail [25]. The possibility of grafting has also been pointed out by Bracco [26]. The here observed ether formation with α close to 70 and 80 % for the model hydrocarbons suggests that similar reactions may occur in α-tocopherol stabilized UHMWPE, in particular since the applied α-tocopherol concentration of 0.1 wt. % as well as the irradiation dose are identical with clinical applications of α-tocopherol stabilized UHMWPE. Grafting of α-tocopherol on UHMWPE upon irradiation by formation of phenolic ethers will also explain both the observed loss of the phenolic OH group and the reduced amount of extractable α-tocopherol. The observed degree of ether formation with α being close to 70 and 80 % for our samples containing 0.1 wt. % α-tocopherol is also consistent with the required amount of α-tocopherol stabilizer in polyethylene, which was found to be ~ 0.075 wt. % for every 10 kGy dose [2].

In UHMWPE, other degradation mechanisms than the observed one for the model hydrocarbons are known to take place as well. Namely, the tocopheroxyl radical may further oxidize and a quinone methide is believed to be formed in a bimolecular reaction [13,26,27]. This quinone methide is unstable and known to dimerize in Diels-Alder-type reactions [13,28]. Such quione methide dimers were successfully extracted from α-tocopherol stabilized LDPE after melt processing [13]. While the formation of the quinone methide intermediate from the tocopheroxyl radical does explain the observed loss of the phenolic OH group, it does not explain the formation of grafted products.

Our results are also fully in line with irradiation induced degradation studies of phenolic antioxidants other than α-tocopherol, where loss of the phenolic OH group [22,29,30] as well as covalently bound phenolic antioxidants are reported [31,32].

5. Conclusion

Studies in model hydrocarbons were performed to elaborate the transformation of the antioxidant α-tocopherol in UHMWPE upon γ-irradiation. When low concentrations of α-tocopherol in alkanes are γ-irradiated at a dosage of 100 kGy, which is typical for the cross-linking of UHMWPE used as material in joint replacement, formation of the corresponding 6-*O*-alkyl-α-tocopherol ether is observed. Even though the applicability of liquid model hydrocarbons for UHMWPE is limited due to different mobilities of the antioxidant and the hydrocarbon radicals, the general reaction mechanisms are comparable. Thus, we infer that the “grafted” α-tocopherol which is reported for γ-irradiated UHMWPE containing α-tocopherol is an 6-*O*-alkyl-α-tocopherol ether where alkyl is the UHMWPE polymer chain. While the observed formation of a quinone methide intermediate can only explain the consumption of the α-tocopherol’s phenol group, ether formation explains the two major observations for irradiated UHMWPE samples containing α-tocopherol in terms of α-tocopherol transformation. Namely i) the consumption of the α-tocopherol’s phenol group upon irradiation, since the phenol group is transformed into an ether and ii) the unsuccessful attempts to extract significant amounts of α-tocopherol transformation products from the irradiated polymer, since the α-tocopherol is chemically bound, i.e. “grafted”, to the polymer via the ether group.

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Table Caption

Table 1: Degree of ether formation α(ether) = n(ether) / n_0(tocopherol) for the γ-irradiation induced reaction between α-tocopherol and the solvent depending on the γ-irradiation dose based on GC-MS (integrated TICs).

Figure Captions

Figure 1: GC-MS chromatogram of the 97.9 kGy irradiated cyclohexane solution of α-tocopherol, with 1,1‘-bicyclohexyl at 1.10 min, α-tocopherol at 15.92 min and 6-*O*-cyclohexyl-α-tocopherol ether 1 at 21.12 min; R' = phytyl-residue $C_{16}H_{33}$. Insert (a) gives the ion trace of the cyclohexyl radical cation at *m*/*z* = 82 and insert (b) shows the chromatogram of the synthetic 6-*O*-cyclohexyl-α-tocopherol ether.

Figure 2: ^{1}H-NMR spectrum of synthetic 6-*O*-cyclohexyl-α-tocopherol ether **1**, top, and the isolated reaction product in the 97.9 kGy irradiated cyclohexane solution of α-tocopherol, bottom. The peaks at 1.53 ppm (bottom, water) and 1.43 ppm (top, unknown) are due to impurities.

Figure 3: GC-MS chromatogram of the 97.9 kGy irradiated *n*-octane solution of α-tocopherol, with α-tocopherol at 15.92 min, the 6-*O*-(4-Octyl)-α-tocopherol ether **2d** at 19.79 min, the 6-*O*-(3-Octyl)-α-tocopherol ether **2c** at 20.15 min, the 6-*O*-(2-Octyl)-α-tocopherol ether **2b** at 20.86 min, and traces of 6-*O*-(1-Octyl)-α-tocopherol ether **2a** at 22.42 min; R' = phytyl-residue $C_{16}H_{33}$. The inserts show the chromatograms of the synthetic 6-*O*-octyl-α-tocopherol ethers **2a**, **2b**, and **2c**.

Scheme 1: Possible mechanism for the formation of 6-*O*-alkyl-α-tocopherol ethers upon γ-irradiation.

Scheme 2: Chemically equivalent CH_2 groups in cyclohexane and *n*-octane and according number of different 6-*O*-alkyl-α-tocopherol ethers.

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Table 1 revised

γ-irradiation dose / kGy	α-tocopherol in cyclohexane α(ether) / %	α-tocopherol in *n*-octane α(ether) / %
0.0	0	0
27.5	34	31
97.9	68	76

Figure 1

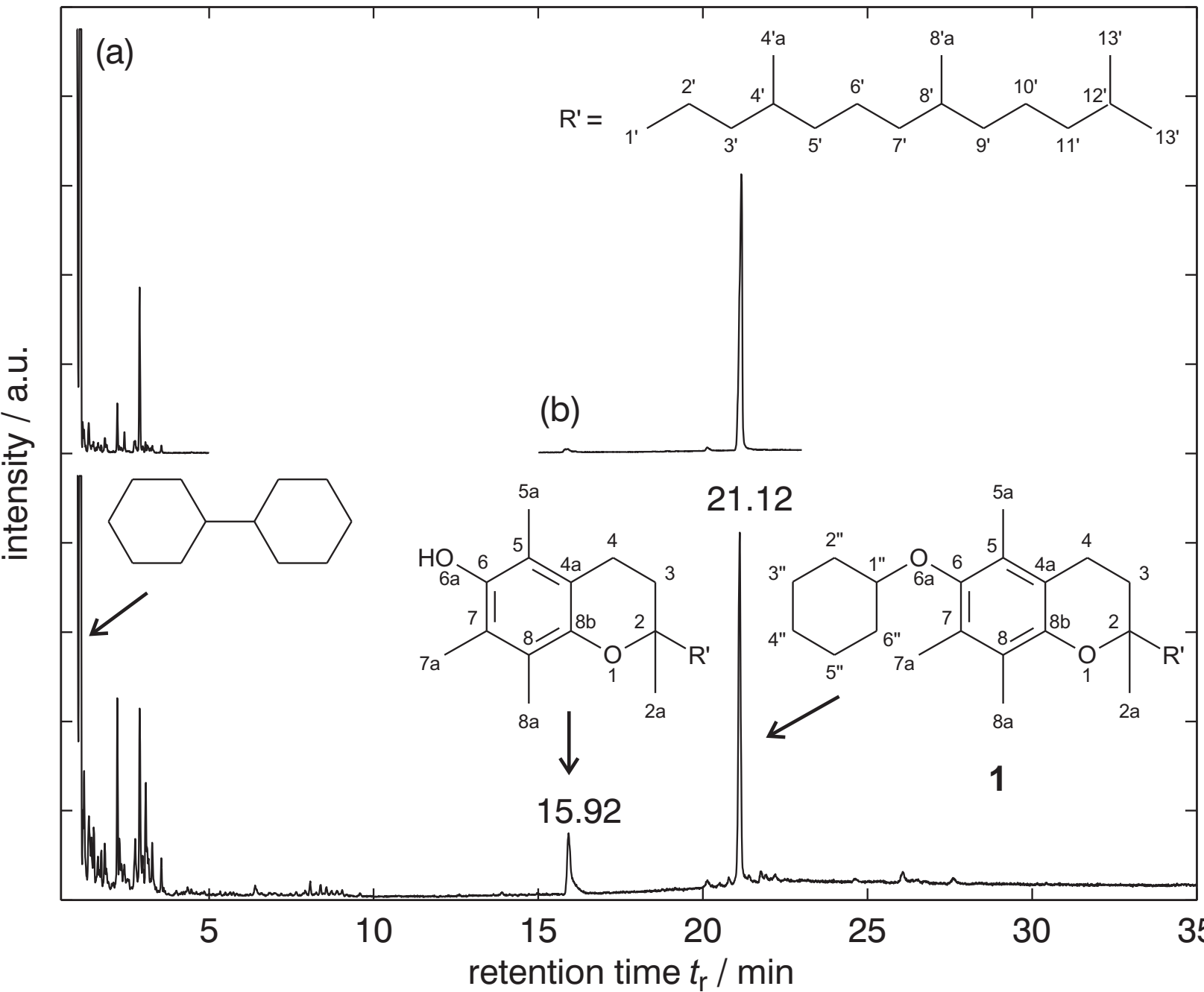

(a)
(b)
R' =
4'a
8'a
13'
2'
4'
6'
8'
10'
12'
1'
3'
5'
7'
9'
11'
13'
21.12
15.92
1
intensity / a.u.
retention time t_r / min
5
10
15
20
25
30
35

Figure 2

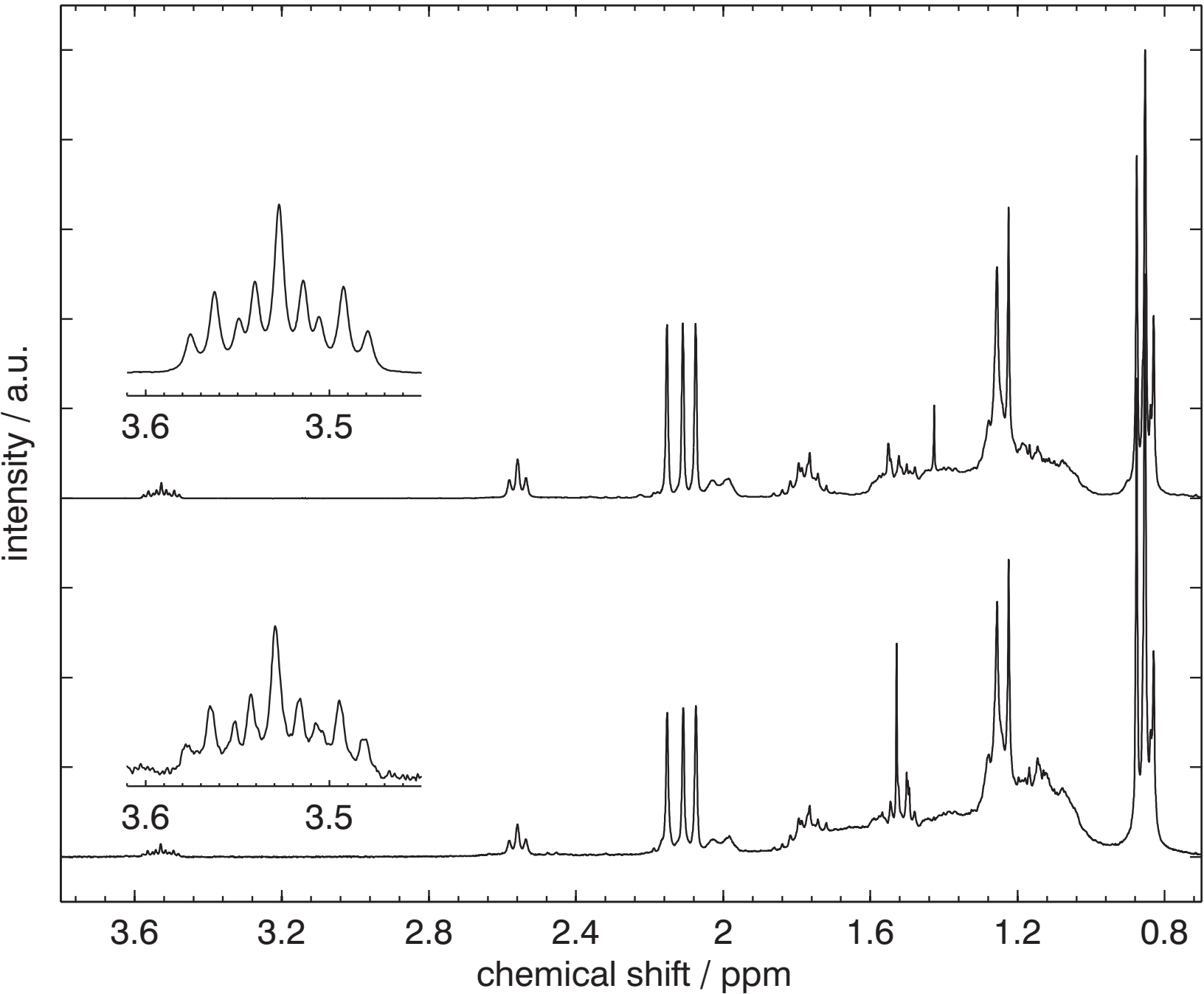
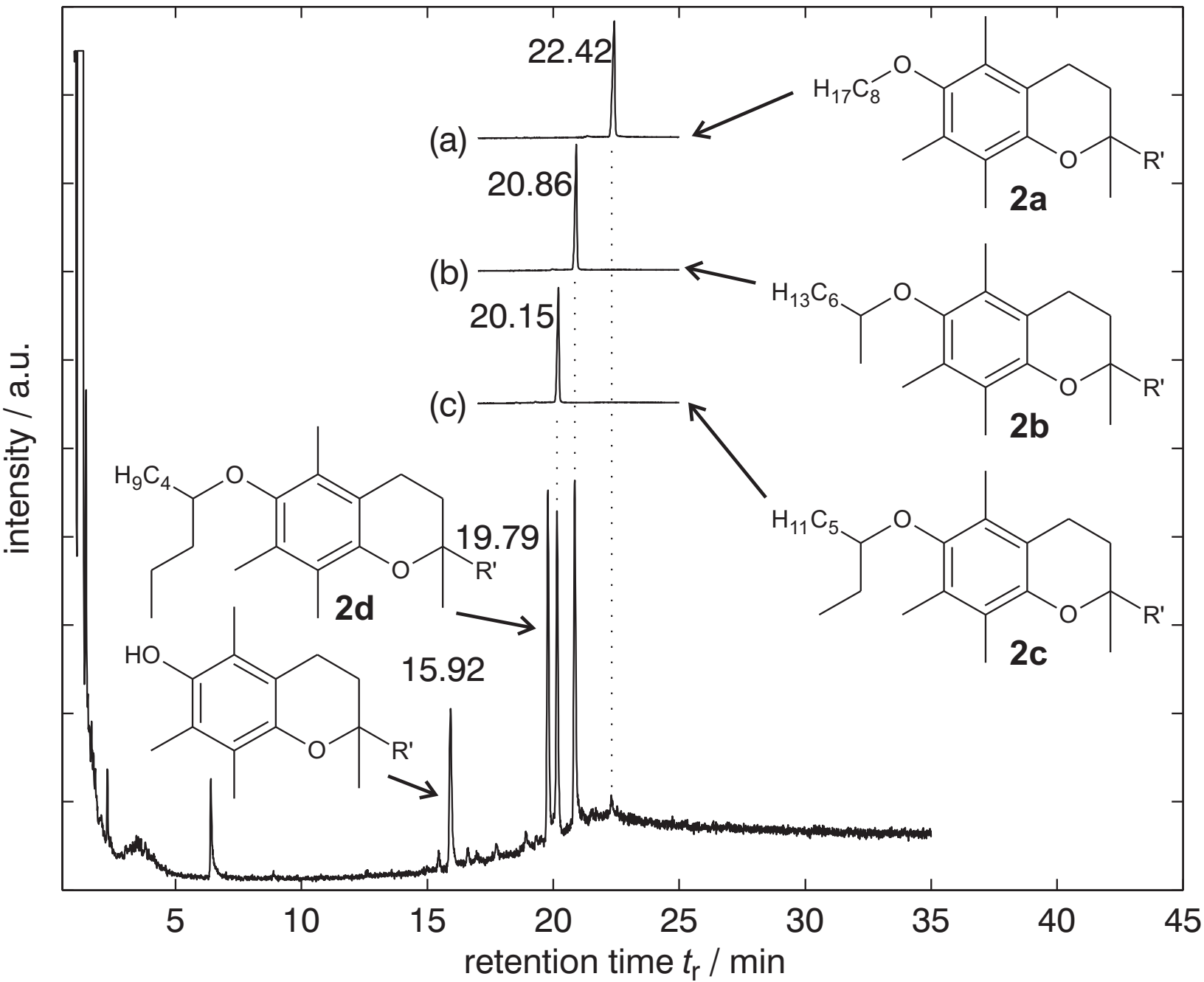
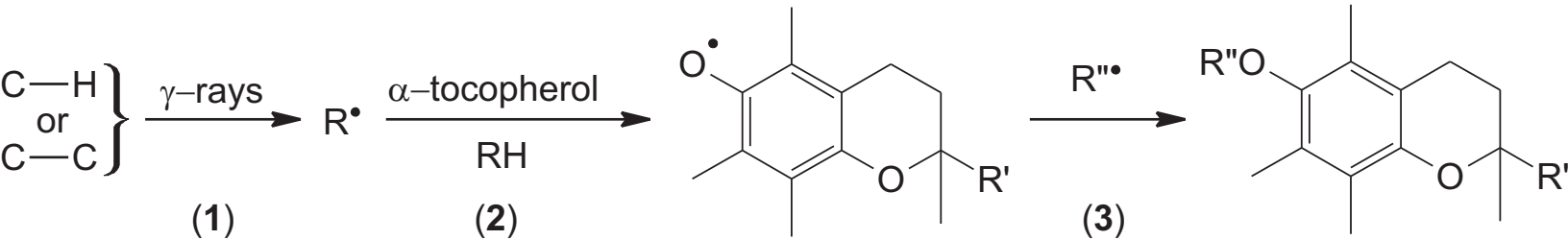

intensity / a.u.
3.6
3.5
3.6
3.5
3.6
3.2
2.8
2.4
2
1.6
1.2
0.8
chemical shift / ppm

Figure 3


22.42
(a)
20.86
(b)
20.15
(c)
19.79
15.92
$H_{17}C_8$
$H_{13}C_6$
$H_{11}C_5$
H_9C_4
HO
O
R'
2a
2b
2c
2d
intensity / a.u.
5
10
15
20
25
30
35
40
45
retention time t_r / min

Scheme 1



Scheme 2