

Article

Controlled Release of Damascone from Poly(styrene-*co*-maleic anhydride)-based Bioconjugates in Functional Perfumery

Damien L. Berthier *, Nicolas Paret, Alain Trachsel, Wolfgang Fieber and Andreas Herrmann

Division Recherche & Développement, Firmenich SA, Route des Jeunes 1, B.P. 239, Genève 8 1211, Switzerland; E-Mails: nicolas.paret@firmenich.com (N.P.); alain.trachsel@firmenich.com (A.T.); wolfgang.fieber@firmenich.com (W.F.); andreas.herrmann@firmenich.com (A.H.)

* Author to whom correspondence should be addressed; E-Mail: damien.berthier@firmenich.com; Fax: +41-22-780-3334.

Received: 23 January 2013; in revised form: 18 February 2013 / Accepted: 19 February 2013 /

Published: 22 February 2013

Abstract: Poly(styrene-*co*-maleic anhydride)s were modified with poly(propylene oxide (PO)-*co*-ethylene oxide (EO)) side chains (Jeffamine[®]) with different EO/PO molar ratios, varying between 0.11 and 3.60. These copolymers were then further functionalized with a β -mercapto ketone of δ -damascone. The obtained poly(maleic acid monoamide)-based β -mercapto ketones were then studied as delivery systems for the controlled release of δ -damascone by retro 1,4-addition. The release of δ -damascone, a volatile, bioactive molecule of the family of rose ketones, was studied by dynamic headspace analysis above a cotton surface after deposition of a cationic surfactant containing fabric softening formulation, as a function of the ethylene oxide (EO)/propylene oxide (PO) molar ratio of the grafted copolymer side chains. The polarity of the EO/PO side chain influenced the release efficiency of the damascone in a typical fabric softening application. PO-rich copolymers and the corresponding poly(styrene-*co*-maleic anhydride) without Jeffamine[®] side chains were found to be less efficient for the desired fragrance release than the corresponding bioconjugate with a EO/PO ratio of 3.60 in the side chain. This copolymer conjugate seemed to represent a suitable balance between hydrophilicity and hydrophobicity to favor the release of the δ -damascone and to improve the deposition of the conjugate from an aqueous environment onto a cotton surface.

Keywords: controlled release; damascones; fragrances; headspace analysis; Jeffamines; polymer conjugates; poly(maleic anhydride); profragrances; retro 1,4-additions; thioethers

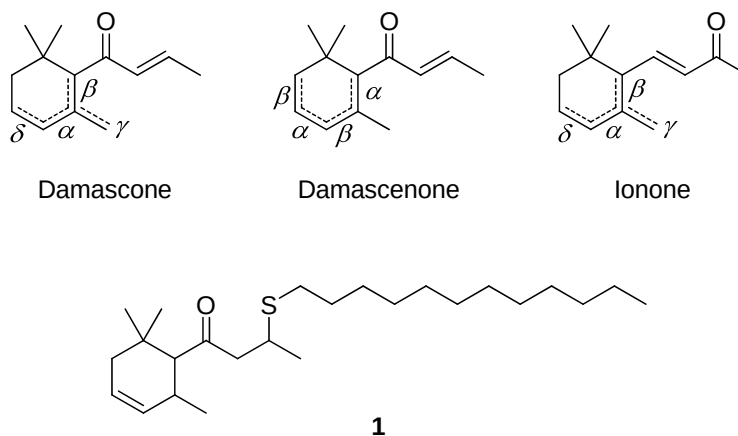
1. Introduction

Fragrances are highly volatile, biologically active organic compounds, which have been used since antiquity to perfume a broad variety of everyday products [1–5]. Because of their high vapor pressures (volatilities), the perception of these molecules is usually limited in time [6,7]. With the performance of commercial body care and household products often being judged on the long-lastingness of perfume perception, the stability of the individual fragrances and their delivery in time are decisive factors for consumers favoring one product over another [8].

Chemical delivery systems, so-called profragrances, have been developed to improve the performance of volatile perfumery molecules in terms of deposition and long-lastingness [9–11]. Mild ambient conditions are used to cleave the covalent bond between the volatile and an (ideally) non-volatile substrate. Reaction conditions allowing covalent bond cleavage and the release of the volatile biomolecule from its precursor comprise changes in temperature or pH, hydrolysis, oxidation and exposure to daylight or enzymes [9–15]. In addition to small molecular precursors, polymer bioconjugates have been investigated for the slow release of volatile compounds [9–11,16–28]. The ease of structural modulation of polymeric materials was expected to allow the selective influence of the properties of the delivery systems and their adaptation to the particular requirements of the formulations into which they were incorporated. The structure of polymers, especially amphiphilic ones, was found to strongly influence the release kinetics of the volatile biomolecules, especially if the formation of self-aggregated structures was possible. The solubility (dispersibility) of the delivery system in aqueous product formulations and the deposition of the conjugates on different surfaces have been identified as important parameters to be considered [23–27].

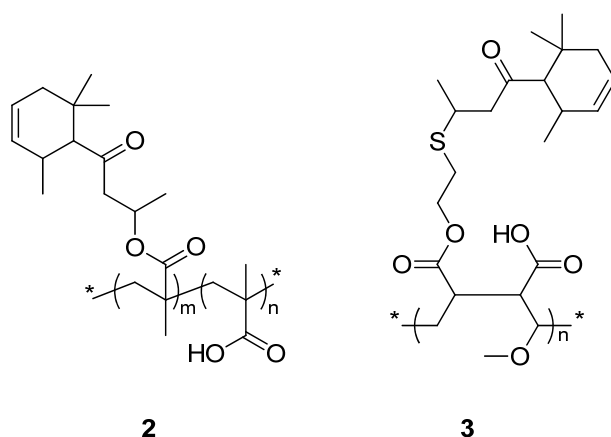
Previous work described Michael-type 1,4-addition of carboxylic acids or thiols to enones [29], allowing the release of damascones, damascenones or ionones, the so-called rose ketones [30,31], in numerous applications of functional perfumery (Figure 1). The general concept works very well [29], and δ -damascone-releasing profragrance **1** has now successfully been commercialized.

Figure 1. Structures of volatile damascones, damascenones and ionones (the suffixes α -, β -, γ - or δ - designate the location of the double bond(s)) and commercially available profragrance **1**.



In a first study, we investigated the pH-dependent release of δ -damascone from amphiphilic random polymethacrylates (such as **2**, Figure 2) and showed that the kinetics of release depended on the molar ratio of a β -acyloxy ketone derivative of δ -damascone and methacrylic acid [20]. This ratio controlled the polarity of the polymer backbone and, thus, its dispersibility in an aqueous environment and, simultaneously, influenced the efficiency of surface adsorption/deposition of the polymer on various substrates.

Figure 2. Examples of polymer conjugates of δ -damascone investigated in previous work [20,27].



In a second study, alternating copolymers of maleic anhydride were modified by the ring opening of the reactive anhydride unit with the hydroxyl group of a precursor resulting from the reaction between δ -damascone and 2-mercaptoethanol [27]. Various alternating copolymers of maleic anhydride with other comonomers (e.g., **3**, Figure 2) were easily prepared in a one-pot, two-step reaction sequence to afford a series of biocompatible delivery systems [27].

The ease of structural modification by choosing suitable comonomers allowed the preparation of copolymers with enhanced surface deposition and/or an increased dispersibility of the conjugates in aqueous media. The release of δ -damascone from the polymer conjugates has been measured in buffered aqueous solution as a function of pH and time, as well as after deposition onto a fabric surface in the presence of a cationic surfactant. The most efficient release of δ -damascone was observed for a poly(maleic acid)-based copolymer with a well-adjusted balance between hydrophilicity (giving rise to high release rates) and hydrophobicity (resulting in increased surface deposition) of the polymer backbone [27].

In addition to the influence of the polymer backbone on the release of δ -damascone, the grafting of specific side chains, which can further influence the release and deposition properties of the delivery systems, has been preliminarily described. For example, the grafting of polyethylene oxide onto poly(maleic anhydride) resulted in an increase of the release rate in water, but a decrease of the deposition on fabric and, thus, a limited overall efficiency of the delivery system in the targeted application [27].

In the present work, we investigated the release of δ -damascone from poly(maleic anhydride)-based conjugates in more detail by extending the structural variety of the polymer structure with respect to our previous work. We thus prepared a series of poly(styrene-*co*-maleic anhydride)s and functionalized

them with ethylene oxide (EO)/propylene oxide (PO) side chains (Jeffamines[®]) with different EO/PO molar ratios. The δ -damascone was grafted via a 2-cysteamine linker by 1,4-addition of the thiol group to the enone double bond of the damascone, followed by the nucleophilic ring opening of the maleic anhydride unit by the amino group. Furthermore, we were interested in particular in how the molar ratio of the EO/PO on the grafted copolymers influenced the release rate of δ -damascone. Besides being grafted onto polymeric profragrance bioconjugates to modify the polarity of the copolymers [20,23,27], EO and/or EO/PO copolymers of different types have also been of interest as physical delivery systems to modify fragrance evaporation, such as in the encapsulation into micellar systems [32–36]. The performance of the different polymer conjugates prepared in this work was investigated by dynamic headspace analysis on dry cotton under realistic conditions of functional perfumery in a fabric softening application [37] under the previously described conditions [27].

2. Experimental Section

2.1. General

Commercially available reagents and solvents were used without further purification, unless stated otherwise. Reactions were carried out in standard glassware under N₂ or Ar, and yields were not optimized. Demineralized H₂O: Millipore-Synergy-185 water purifier. Infrared (IR) spectra: Perkin-Elmer-1600-FTIR spectrometer; $\tilde{\nu}$ of weak (w), medium (m) or strong (s) bands in cm^{−1}. ¹H- and ¹³C-nuclear magnetic resonance (NMR) spectra: Bruker 400 MHz Avance III spectrometer; δ in ppm downfield from Me₄Si as internal standard. Standard pulse sequences and parameters were used for one-dimensional ¹H- and ¹³C-NMR experiments and for two-dimensional, gradient selected correlation spectroscopy (COSY), ¹H, ¹³C-HSQC and ¹H, ¹³C-heteronuclear multiple bond correlation (HMBC) experiments, respectively.

2.2. Analytical Size-Exclusion Chromatography (SEC)

Size-exclusion chromatography (SEC) analyses were carried out at room temperature (*ca.* 22 °C) on a Viscotek GPC max VE 2001 GPC Solvent Sample Module connected to a Viscotek UV detector 2500, a Viscotek VE3580 RI detector and a Viscotek-270-Dual-Detector viscometer. Samples were eluted from a Macherey-Nagel VA 300/7.7 Nucleogel GPC 500-5 column at a flow rate of 1.0 mL min^{−1} with tetrahydrofuran (THF, high performance liquid chromatography (HPLC)-grade). Universal calibrations were performed using commercial poly(styrene) standards. The polymer standard (*ca.* 40 mg) was accurately weighed and dissolved in THF (10 mL); then, these solutions (100 μ L) were injected for the calibration. Molecular weight averages and polydispersity indices (PDIs) of the different polymers are listed in Table 2 below.

2.3. Preparation of 3-(2-Aminoethylthio)-1-(2,6,6-trimethyl-cyclohex-3-enyl)-butan-1-one (4) and 3-((2-((4-oxo-4-(2,6,6-Trimethylcyclohex-3-en-1-yl)butan-2-yl)amino)ethyl)thio)-1-(2,6,6-trimethylcyclohex-3-en-1-yl)butan-1-one (5)

In a 100 mL round-bottomed flask, (*E*)-1-(2,6,6-trimethylcyclohex-3-enyl)but-2-en-1-one (δ -damascone, 20.0 g, 104.0 mmol), triethylamine (14.5 mL, 104.0 mmol) and

2-aminoethanethiol hydrochloride (11.8 g, 104.0 mmol) were dissolved in ethanol (50 mL) to give a colorless solution. 2,3,4,6,7,8,9,10-Octahydropyrimido[1,2-a]azepine (1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1.6 g, 10.4 mmol) was added. The reaction mixture was then stirred at room temperature overnight. Cyclohexane (30 mL) was added to the reaction mixture to give a precipitate, which was removed by filtration. Ethanol was evaporated, and the reaction mixture was washed with NaCl (2 M, 2×50 mL), NaOH (10^{-3} M, 40 mL) and H₂O. The organic layer was dried with MgSO₄, filtered and concentrated to give a yellow oil of **4** and **5** in a ratio of 1.2:1 as a mixture of diastereoisomers ($m = 27$ g). ¹H-NMR (CDCl₃, 400 MHz) **4**: δ 5.53 (m, 1H), 5.44 (m, 1H), 3.32 (m, 1H), 2.91 (m, 1H, diastereoisomer 1), 2.72 (m, 2H, diastereoisomer 2), 2.66 (br m, 1H), 2.53 (m, 1H, diastereoisomer 1), 2.51 (m, 1H), 2.50 (m, 1H), 2.22 (m, 1H), 1.96 (m, 1H), 1.69 (m, 1H), 1.31 (m, 3H), 1.00 or 0.98 (m, 3H), 0.95 (m, 3H) and 0.89 (m, 3H) ppm. ¹H-NMR (CDCl₃, 400 MHz) **5**: δ 5.53 (m, 2H), 5.44 (m, 2H), 3.32 (m, 1H), 3.18 (m, 1H), 2.91 (m, 1H, diastereoisomer 1), 2.86 (m, 1H), 2.77 (m, 1H, diastereoisomer 1), 2.75 (m, 1H), 2.72 (m, 2H, diastereoisomer 2), 2.71 (m, 2H), 2.61 (m, 2H, diastereoisomer 2), 2.53 (m, 1H, diastereoisomer 1), 2.50 (m, 1H), 2.46 (m, 1H, diastereoisomer 1), 2.24 (m, 1H), 2.22 (m, 1H), 1.96 (m, 2H), 1.69 (m, 2H), 1.31 (m, 3H), 1.10 (m, 3H), 1.00 (m, 3H), 0.98 (m, 3H), 0.95 (m, 6H) and 0.89 (m, 6H) ppm. ¹³C-NMR (CDCl₃, 100.6 MHz) **4**: δ 212.2 (s), 131.8 (d), 124.2 (d), 62.9 (d), 55.2 (t), 41.7 (t), 41.3 (br t), 34.8 (br t), 34.0 (d), 33.1 (s), 31.7 (d), 29.8 (q), 21.9 (q), 20.7 (q), 19.9 (q) ppm. ¹³C-NMR (CDCl₃, 100.6 MHz) **5**: δ 214.1 (s), 212.2 (s), 131.8 (d), 124.2 (d), 62.9 (d), 55.2 (t), 54.9 (t), 48.5 (d), 46.1 (t), 41.7 (t), 34.0 (d), 33.1 (s), 31.7 (d), 31.3 (t), 29.8 (q), 21.9 (q), 20.7 (q), 20.4 (q) and 19.9 (q) ppm. IR (neat): 3387w, 3317w, 3018m, 2957s, 2928m, 2871m, 2830m, 1703s, 1652m, 1457m, 1386m, 1366s, 1280w, 1250w, 1212w, 1194w, 1153m, 1116m, 1080m, 1039w, 998m, 953w, 932w, 896w, 842w, 787w, 691s, 683s and 641m cm⁻¹.

2.4. General Procedure to Prepare Copolymers of Styrene, Maleic Anhydride and 4-oxo-4-(ω -(2-Methoxyethyl)[poly(ethylene oxide)-co-poly(propylene oxide)]ethyl}amino)but-2-enoic Acid

In a 50 mL round-bottomed flask, poly(styrene-co-maleic anhydride) (**6**, 4.0 g, 18.78 mmol with respect to the anhydride group) and α -(2-aminoethyl)- ω -(2-methoxyethyl)-poly(propylene glycol-co-ethylene glycol) (**7–9**, Table 1, 1.88 mmol) were dissolved in acetone (20 mL) to give a yellow solution. The reaction mixture was stirred at 50 °C overnight. Copolymers **10–12** were obtained by precipitation from water, filtered and dried under vacuum at 50 °C for 24 h.

2.4.1. Copolymer of Styrene, Maleic Anhydride and 4-oxo-4-(ω -(2-Methoxyethyl)[poly(ethylene oxide)-co-poly(propylene oxide)]ethyl}amino)but-2-enoic Acid (**10**) (Obtained by Grafting of Copolymer **7** with EO/PO = 0.11)

Precipitation yielded a white solid (5.01 g, Y = 99%). ¹H-NMR (Acetone-d₆, 400 MHz): δ 7.3 (m, 5H), 4.5–3.0 (m, 4.4H), 1.5–1.0 (m, 2.9H). ¹³C-NMR (Acetone-d₆, 100.6 MHz): δ 173.8 (s), 129.6 (d), 77.3 (t), 76.1 (d), 74.0 (t), 73.8 (t), 52.9 (br d), 43.3 (br d), 41.5 (br d) and 17.9 (q). IR (neat): 3594w, 3029w, 2972w, 2932w, 2876w, 1855w, 1775m, 1728m, 1602w, 1583w, 1540w, 1494w, 1454m, 1374w, 1338w, 1218w, 1159m, 1078m, 1030w, 947m, 917m, 847w, 763m, 729w and 700s cm⁻¹.

2.4.2. Copolymer of Styrene, Maleic Anhydride and 4-oxo-4-({ ω -(2-Methoxyethyl)[poly(ethylene oxide)-*co*-poly(propylene oxide)]ethyl}amino)but-2-enoic Acid (**11**) (Obtained by Grafting of Copolymer **8** with EO/PO = 0.14)

Precipitation afforded a white solid (7.40 g, Y = 99%). $^1\text{H-NMR}$ (Acetone- d_6 , 400 MHz): δ 7.3 (m, 5H), 4.0–3.0 (m, 10.5H) and 1.6–0.8 (m, 8.7H). $^{13}\text{C-NMR}$ (Acetone- d_6 , 100.6 MHz): δ 173.3 (br s), 129.5 (br d), 76.2 (d), 76.1 (d), 75.9 (d), 74.0 (t), 73.8 (t), 73.7 (t), 71.3 (t), 43.5 (br d) and 17.9 (q). IR (neat): 3590w, 3060w, 3028w, 2970w, 2929w, 2874w, 1855w, 1776m, 1728m, 1602w, 1583w, 1540w, 1494w, 1454m, 1374w, 1338w, 1218w, 1160m, 1080m, 1030w, 945m, 917m, 847w, 762m and 699s cm^{-1} .

2.4.3. Copolymer of Styrene, Maleic Anhydride and 4-oxo-4-({ ω -(2-Methoxyethyl)[poly(ethylene oxide)-*co*-poly(propylene oxide)]ethyl}amino)but-2-enoic Acid (**12**) (Obtained by Grafting of Copolymer **9** with EO/PO = 3.60)

Precipitation afforded a white solid (7.20 g, 97%). $^1\text{H-NMR}$ (Acetone- d_6 , 400 MHz): δ 7.29 (m, 5H), 4.0–3.0 (m, 14.5H) and 1.6–0.8 (m, 3H) ppm. $^{13}\text{C-NMR}$ (Acetone- d_6 , 100.6 MHz): δ 173.3 (s), 129.6 (d), 75.8 (t), 75.6 (d), 72.7 (t), 71.8 (t), 71.6 (t), 71.5 (t), 71.3 (t), 71.1 (t), 69.4 (t), 43.2 (br d) and 17.8 (q) ppm. IR (neat): 3591w, 3060w, 3020w, 2971w, 2930w, 2874w, 1853w, 1774m, 1727m, 1600w, 1581w, 1541w, 1493w, 1453m, 1375w, 1338w, 1218w, 1160m, 1080m, 945m, 917m, 847w, 762m and 699s cm^{-1} .

2.5. General Procedure to Prepare Copolymers of Styrene, 4-oxo-4-({ ω -(2-Methoxyethyl)[poly(ethylene oxide)-*co*-poly(propylene oxide)]ethyl}amino)but-2-enoic Acid and 4-oxo-4-[[2-([4-oxo-4-(2,6,6-trimethylcyclohex-3-en-1-yl)butan-2-yl]thio)ethyl}amino]but-2-enoic Acid

In a 100 mL round-bottomed flask, copolymers **10–12** (4.65 mmol with respect to the anhydride groups) and a mixture of **4** and **5** (2.35 g, at a ratio of 1.2:1, corresponding to 4.68 mmol of **4**) were dissolved in acetone (40 mL) to give a yellow solution. The reaction mixture was stirred at 50 °C overnight. Copolymers **13–15** were obtained by precipitation from *n*-heptane, filtered and dried under vacuum at 50 °C for 24 h.

2.5.1. Copolymer of Styrene, 4-oxo-4-({ ω -(2-Methoxyethyl)[poly(ethylene oxide)-*co*-poly(propylene oxide)]ethyl}amino)but-2-enoic Acid (EO/PO = 0.11) and 4-oxo-4-[[2-([4-oxo-4-(2,6,6-Trimethylcyclohex-3-en-1-yl)butan-2-yl]thio)ethyl}amino]but-2-enoic Acid (**13**)

Prepared from **10** (1.31 g), precipitation afforded a white solid (2.44 g, Y = 98%). $^1\text{H-NMR}$ (Acetone- d_6 , 400 MHz): δ 7.15 (br m, 5H), 5.53 (m, 1H), 5.44 (m, 1H), 4.5–3.2 (m, 6H), 3.0 (m, 1H), 2.9–2.6 (m, 4H) 2.5 (m, 2H), 2.3 (m, 2H), 1.99 (m, 1H), 1.7 (m, 2H), 1.3 (m, 4H), 1.1 (m, 3H), 1.00 or 0.98 (m, 3H) and 0.95 (m, 7H) ppm. $^{13}\text{C-NMR}$ (Acetone- d_6 , 100.6 MHz): δ 212.5 (s), 132.7 (d), 129.2 (br d), 125.1 (d), 77.4 (t), 76.1 (d), 74.1 (t), 73.8 (t), 63.0 (d), 56.0 (t), 55.8 (t), 52.1 (t), 43.6 (d), 40.7 (t), 35.1 (d), 34.8 (d), 33.7 (d), 32.6 (d), 31.9 (t), 22.3 (q), 21.2 (q), 20.3 (q) and 17.8 (q) ppm. IR (neat): 3406w, 3059w, 3020m, 2959m, 2931m, 2871m, 2830w, 1702s, 1648m, 1601m, 1548s, 1494m,

1453s, 1387m, 1366s, 1298w, 1269w, 1248w, 1212w, 1153m, 1113m, 1088m, 999m, 935w, 903w, 843w, 799w, 761m, 698s and 641m cm^{-1} .

2.5.2. Copolymer of Styrene, 4-oxo-4-({ ω -(2-Methoxy ethyl)[poly(ethylene oxide)-*co*-poly(propylene oxide)]ethyl}amino)but-2-enoic Acid (EO/PO = 0.14) and 4-oxo-4-[2-([4-oxo-4-(2,6,6-Trimethylcyclohex-3-en-1-yl)butan-2-yl]thio)ethyl}amino]but-2-enoic Acid (**14**)

Prepared from **11** (2.00 g), precipitation afforded a white solid (2.78 g, Y = 88%). $^1\text{H-NMR}$ (Acetone- d^6 , 400 MHz): δ 7.15 (br m, 5H), 5.55 (m, 1H), 5.48 (m, 1H), 4.0–3.2 (m, 10.7H), 3.12 (m, 1H), 2.9–2.6 (m, 4H) 2.48 (m, 2H), 2.33 (m, 1H), 1.99 (m, 1H), 1.89 (m, 0.5H), 1.7 (m, 2H), 1.3 (m, 4H), 1.1 (m, 7H), 1.03 or 0.98 (m, 3H) and 0.95 (m, 6H) ppm. $^{13}\text{C-NMR}$ (Acetone- d^6 , 100.6 MHz): δ 212.5 (s), 132.6 (d), 129.1 (br d), 125.1 (d), 76.2 (d), 76.0 (d), 75.9 (d), 74.0 (t), 73.8 (t), 71.3 (t), 63.0 (d), 55.9 (t), 55.5 (t), 42.3 (t), 35.1 (d), 34.7 (d), 33.7 (s), 32.6 (d), 32.5 (d), 22.2 (q), 21.1 (q), 20.2 (q) and 17.90 (q) ppm. IR (neat): 3397w, 3059w, 3020m, 2964m, 2931m, 2870m, 1703s, 1649m, 1601m, 1553s, 1494m, 1453s, 1386m, 1369s, 1297w, 1269w, 1249w, 1212w, 1151m, 1097s, 1009m, 933w, 904w, 844w, 802w, 762m, 698s and 645m cm^{-1} .

2.5.3. Copolymer of Styrene, 4-oxo-4-({ ω -(2-Methoxy ethyl)[poly(ethylene oxide)-*co*-poly(propylene oxide)]ethyl}amino)but-2-enoic Acid (EO/PO = 3.60) and 4-oxo-4-[2-([4-oxo-4-(2,6,6-Trimethylcyclohex-3-en-1-yl)butan-2-yl]thio)ethyl}amino]but-2-enoic Acid (**15**)

Prepared from **12** (2.01 g), precipitation afforded a white solid (3.14 g, Y = 98%). $^1\text{H-NMR}$ (Acetone- d^6 , 400 MHz): δ 7.20 (m, 5H), 5.58 (m, 1H), 5.48 (m, 1H), 4.0–3.0 (m, 17.5H), 3.12 (m, 0.5H), 2.9–2.6 (m, 4H) 2.48 (m, 2H), 2.34 (m, 1H), 1.99 (m, 1H), 1.89 (m, 0.5H), 1.7 (m, 2H), 1.3 (m, 4H), 1.1 (m, 3H), 1.03 or 0.98 (m, 3H) and 0.95 (m, 6H) ppm. $^{13}\text{C-NMR}$ (Acetone- d^6 , 100.6 MHz): δ 212.5 (s), 132.7 (d), 129.1 (d), 127.1 (d), 125.1 (d), 75.8 (t), 75.6 (d), 72.7 (t), 71.8 (t), 71.6 (t), 71.5 (t), 71.3 (t), 69.4 (t), 63.0 (d), 55.9 (t), 42.3 (t), 35.1 (d), 33.7 (s), 32.6 (d), 22.2 (q), 21.1 (q), 20.3 (q) and 17.8 (q) ppm. IR (neat): 3396w, 3060w, 3020m, 2956m, 2929m, 2870s, 1702s, 1649m, 1601m, 1553s, 1494m, 1454s, 1386m, 1366s, 1298w, 1249w, 1212w, 1094s, 1040m, 999m, 951w, 844w, 802w, 762m, 699s and 642m cm^{-1} .

2.5.4. Copolymer of Styrene and 4-oxo-4-[2-([4-oxo-4-(2,6,6-Trimethylcyclohex-3-en-1-yl)butan-2-yl]thio)ethyl}amino]but-2-enoic Acid (**16**)

In a 50 mL round-bottomed flask, a mixture of **4** and **5** (4.00 g, at a ratio of 1.2:1, corresponding to 7.98 mmol of **4**) and poly(styrene-*co*-maleic anhydride) **6** (2.00 g, 8.44 mmol of maleic anhydride units) were dissolved in acetone (40 mL) to give a yellow solution. The reaction mixture was stirred at 50 °C overnight. The solvent was partially evaporated, and the polymer was precipitated in water to afford a white solid after filtration (m = 4.26 g, Y = 99%). $^1\text{H-NMR}$ (Acetone- d^6 , 400 MHz): δ 7.17 (m, 5H), 5.55 (m, 1H), 5.48 (m, 1H), 3.51 (m, 1H), 3.35 (m, 2H), 3.16 (m, 0.5H), 2.99 (m, 1H), 2.82 (m, 3H), 2.66 (m, 1H), 2.48 (m, 2H), 2.34 (m, 1H), 1.99 (m, 1H), 1.89 (m, 0.5H), 1.7 (m, 2H), 1.3 (m, 4H), 1.03 or 0.98 (m, 3H) and 0.95 (m, 6H) ppm. $^{13}\text{C-NMR}$ (Acetone- d^6 , 100.6 MHz): δ 212.5 (s), 132.7 (d), 129.1 (br d), 125.1 (d), 63.0 (d), 55.8 (t), 42.3 (t), 34.9 (d), 33.7 (s), 32.6 (d),

22.3 (q), 21.2 (q) and 20.3 (q) ppm. IR (neat): 3395w, 3059w, 3019m, 2957m, 2929m, 2871m, 2829w, 1702s, 1652w, 1601m, 1547m, 1494m, 1453s, 1387m, 1365s, 1297w, 1269w, 1247w, 1212w, 1153w, 1084w, 1031w, 999m, 896w, 844w, 762m, 698s and 639m cm^{-1} .

2.6. Preparation of Aqueous Surfactant Emulsions

A cationic triethanolamine (TEA)-esterquat surfactant formulation was prepared from the following ingredients: Stepantex[®] VK90 (Stepan) 16.5%, an aqueous solution of calcium chloride (10%) 0.2% and water 83.3%. Depending on the δ -damascone content of the polymers, a total of 1.26 to 1.88% of poly(maleic acid)-based copolymers **13–16** was added to the softener formulation (5.00 g) in order to release a total amount of 8.7 mg of δ -damascone from each sample. All values are given in % by weight.

2.7. Procedure for Polymer Deposition on Cotton and Dynamic Headspace Analysis [27]

In a small vial, poly(maleic acid)-based copolymers **13–16**, dissolved in ethyl acetate (0.5 mL, **13**: 26.9 mg, **14**, **15**: 34.0 mg, **16**: 22.7 mg, all releasing a total amount of 8.7 mg of δ -damascone) were added to the aqueous surfactant formulation (1.80 g), and the resulting mixtures were stirred overnight. The emulsions were then placed in a beaker (1 L) and diluted with demineralized cold tap water (600 g). One cotton sheet (Eidgenössische Materialprüfanstalt (EMPA, Switzerland), cotton test cloth Nr. 221, cut to *ca.* 12 × 12 cm sheets (average mass *ca.* 3.12 g and prewashed with an unperfumed detergent powder) was added to each beaker. The sheet was manually stirred for 3 min, left standing for 2 min and then wrung out by hand and weighed (average mass *ca.* 7.0 g) to ensure a constant amount of residual water. A solution with an equimolar amount of unmodified δ -damascone (8.7 mg in 0.5 mL of acetone) was added to another sample of the fabric softener formulation (1.80 g), which was used as the reference sample and treated as described above. All cotton sheets were line dried for 1 day.

Each of the line-dried cotton sheets was individually placed inside a headspace sampling cell (with a total internal volume of *ca.* 160 mL). The sampling device was thermostatted at 25 °C and exposed to a constant flow of air (*ca.* 200 mL min^{-1}). The air was filtered through active charcoal and aspirated through a saturated solution of NaCl to ensure a constant humidity of *ca.* 75%. For 2 h, the volatiles were adsorbed onto a waste Tenax[®] cartridge and then for 15 min onto a clean Tenax[®] cartridge (corresponding to a total sample volume of 3 L of air). The sampling was repeated twice every 2 h (105 min of trapping on the waste cartridge and 15 min of sampling onto a clean cartridge); the waste cartridges were discarded. The other cartridges were thermally desorbed on a Perkin Elmer TurboMatrix ATD 350 desorber coupled to an Agilent Technologies 7890A gas chromatograph equipped with a HP-1 capillary column (30 m, i.d. 0.32 mm, film thickness 0.25 μm) and a flame ionization detector. The volatiles were analyzed using a two-step temperature gradient starting from 60 °C to 130 °C at 15 °C min^{-1} and then heating to 220 °C at 40 °C min^{-1} . The injection temperature was at 250 °C and the detector temperature at 250 °C. External standard calibrations were carried out using five different concentrations of δ -damascone in acetone (varying between 7.09×10^{-5} and 2.63×10^{-2} mol L^{-1}). Each calibration solution (0.2 μL) was injected onto three clean Tenax[®] cartridges. All cartridges were then desorbed immediately under the same conditions as those resulting

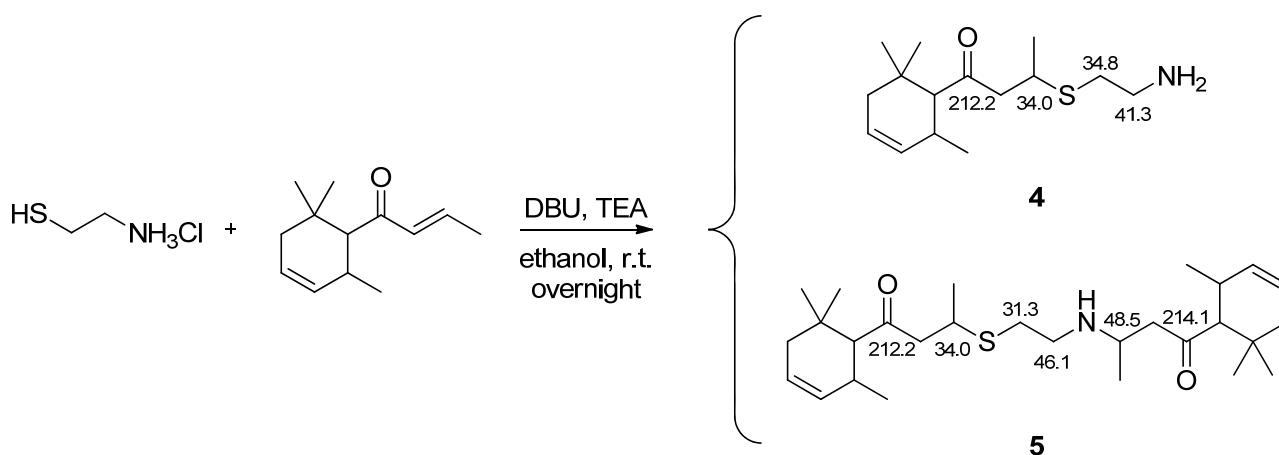
from the headspace sampling (see above). Since the quantities of released compounds were monitored down to very low concentrations, the calibration curve was forced through the origin of the coordinate system. Plotting the concentrations (in ng L^{-1}) against the peak areas gave a straight line ($y = 1.452 x$) with a correlation coefficient of $r^2 = 1.0000$. All experiments were carried out in duplicate.

3. Results and Discussion

3.1. Preparation of the δ -Damascone-Releasing Unit

δ -Damascone was conjugated to the poly(styrene-*co*-maleic anhydride) backbone by 1,4-Michael type addition of the thiol group from cysteamine hydrochloride onto the enone double bond to give the δ -damascone-releasing unit **4** (Scheme 1). DBU was used as a catalyst, and triethylamine was added to deprotonate the ammonium function of the linker to facilitate its solubility in ethanol. The addition of the cysteamine on the enone can theoretically occur by reaction of either the NH_2 or $-\text{SH}$ group. We expected that the more stable product **4** was preferentially formed. To verify the selectivity between the two possible reactions, the crude reaction product was characterized by FTIR and NMR spectroscopy.

Scheme 1. Synthesis of 3-((2-aminoethyl)thio)-1-(2,6,6-trimethylcyclohex-3-en-1-yl)butan-1-one (**4**) as δ -damascone-releasing unit and formation of diadduct (**5**).



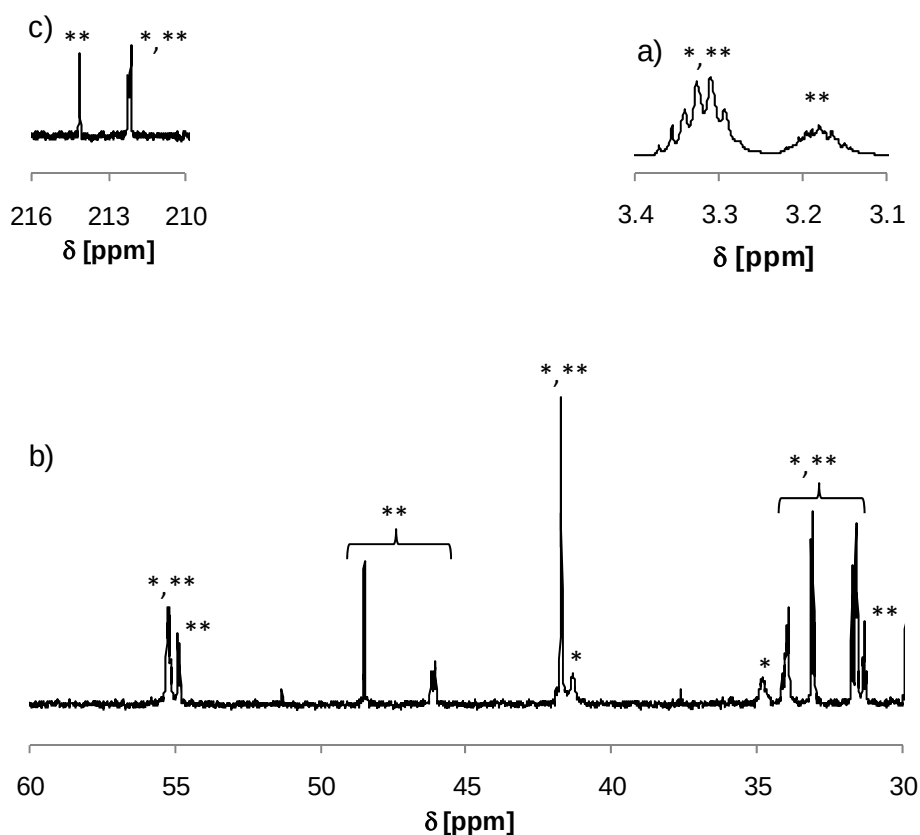
^1H -NMR spectroscopy showed that the reaction was not selective (see Figure 3a and Experimental Section).

Interpretation of the ^{13}C -NMR spectrum revealed that a mixture of the desired compound **4** and diaddition product **5** was obtained (Figure 3b). Broad triplets at 34.8 and 41.3 ppm correspond to the two CH_2 groups of the thioether with a terminal NH_2 group. A signal, which would correspond to a CH_2 group next to the $-\text{SH}$ function, was not detected. This assignment was confirmed by the absence of a peak between 2600 and 2650 cm^{-1} in the IR spectrum, which would indicate the presence of a thiol group. In contrast, the presence of two peaks at 3,317 and 3,387 cm^{-1} confirmed the presence of the NH_2 group in **4**.

Subsequently, a comprehensive 2D-NMR analysis was carried out. The two triplets observed at 31.3 and 46.1 ppm in the ^{13}C -NMR spectrum further confirmed the presence of the diaddition

product **5**. The carbonyl groups of the δ -damascone unit give rise to signals at 212.2 ppm (if linked via a thioether) and 214.1 ppm (if linked via a secondary amine, Figure 3c). Integration of these two signals resulted in a ratio of 2.2:1. After subtraction of the integral of the signal at 214.1 ppm (which corresponds exclusively to compound **5**) from that at 212.2 ppm (corresponding to both compounds **4** and **5**), a molar ratio of 1.2 to 1 was calculated for **4** and **5**. Similar values were obtained from integration of signals in the ^1H -NMR spectrum. Because diaddition product **5** does not react with the maleic anhydride of the polymer backbone, its presence should not be a problem for the next reaction step. It can easily be removed during the purification of the modified copolymer.

Figure 3. Enlargements of the ^1H -NMR (a) and ^{13}C -NMR (b,c) spectra of the mixture of compounds **4** (*) and **5** (**).



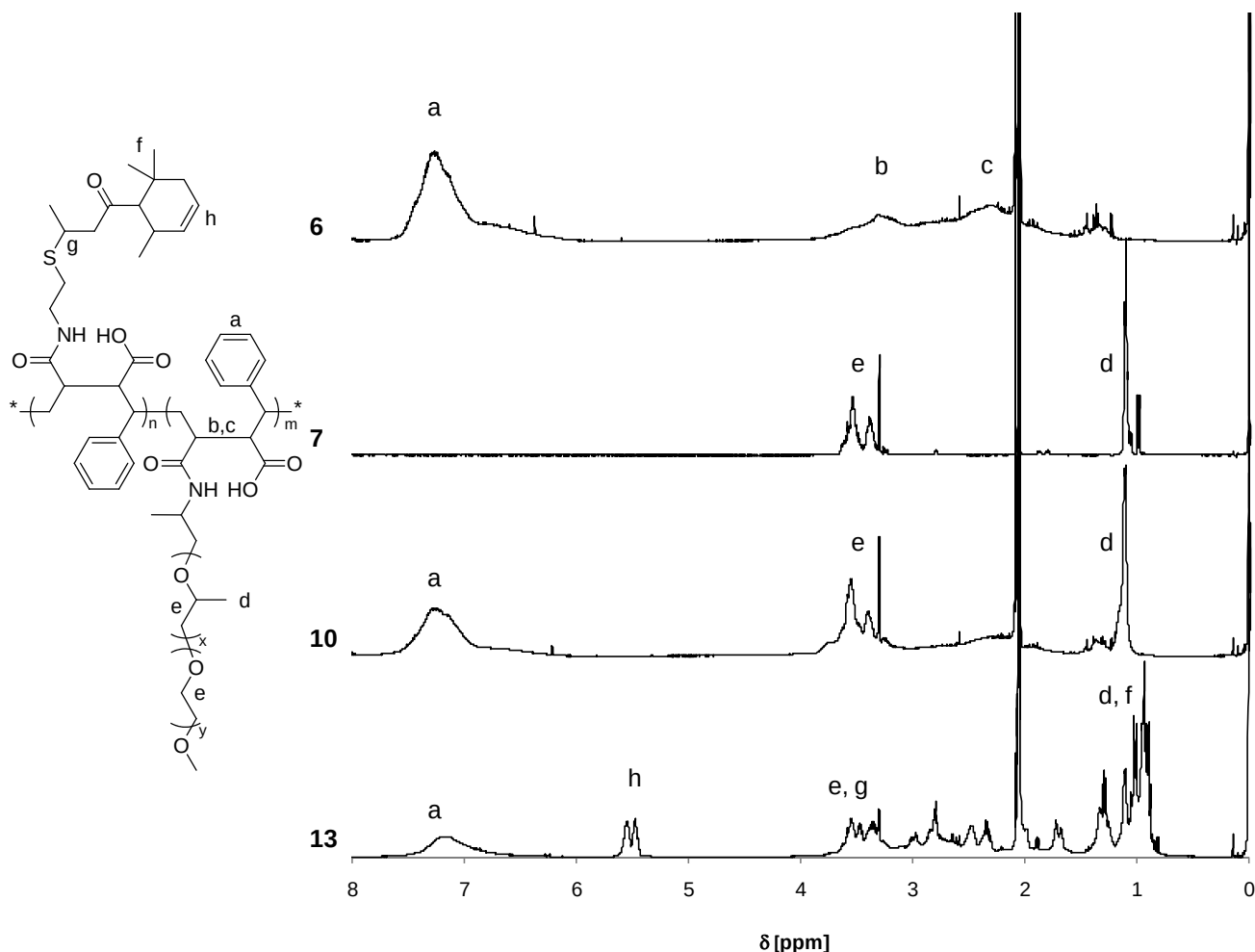
3.2. Synthesis of Copolymers

To determine the styrene/maleic anhydride (S/MA) molar ratio, commercially available copolymer **6** was analyzed by ^1H -NMR spectroscopy. Integration of the signals centered at 7.20 ppm (corresponding to the aromatic ring of styrene (a, Figure 4)) and those at 2.20 and 3.30 ppm (resulting from the styrene and the maleic anhydride backbone (b and c, respectively, Figure 4)) showed that the S/MA molar ratio was around 1.1, which is close to the value of 1.3 given by the supplier. Nevertheless, the peaks are not well resolved, and quantitative analysis is difficult.

According to this ratio, the structure of copolymer **6** in Scheme 2 is represented as an alternating copolymer with a S/MA molar ratio of 1. With 1.1 equivalents of styrene and 1 equivalent of maleic anhydride, the molecular weight of the repeating unit corresponded to $213.51 \text{ g mol}^{-1}$. The number

average molecular weight M_n of **6** was measured by analytical SEC to be 2100 g mol^{-1} , in contrast to a value of 1600 g mol^{-1} given by the supplier. This molecular weight corresponds to a polymer consisting on average of 10 repeat units.

Figure 4. ^1H -NMR spectra of copolymers **6**, **7**, **10** and **13** recorded in acetone- d_6 .



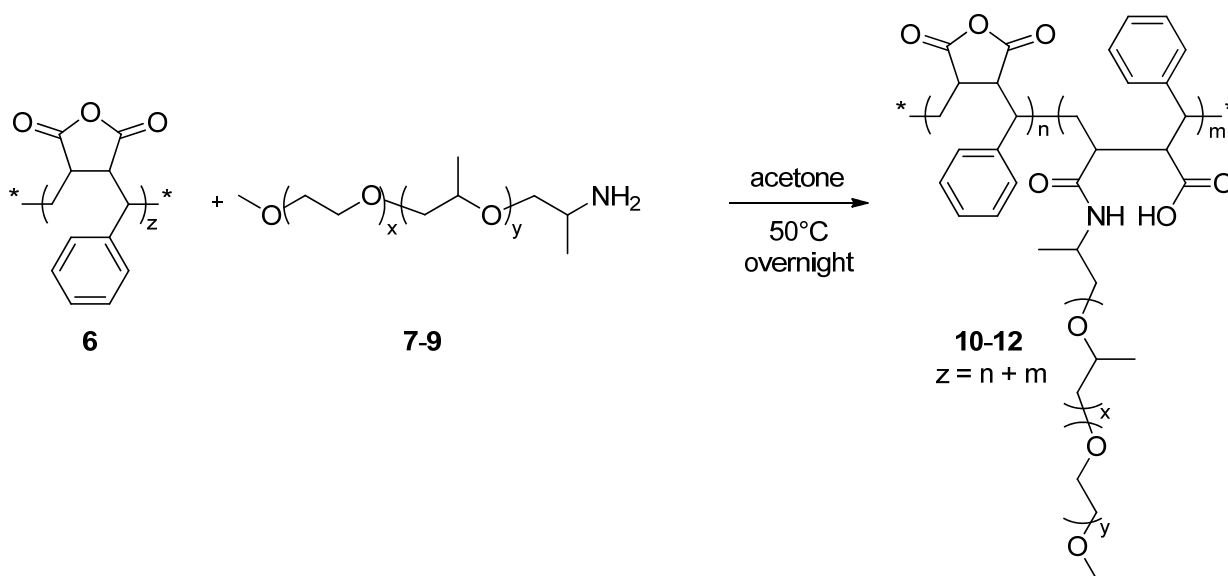
Amino functionalized ethylene oxide (EO)/propylene oxide (PO) copolymers (Jeffamine[®]) (**7–9** in Scheme 2) are commercially available, and their molecular composition was given by the supplier as illustrated in Table 1. Their EO/PO molar ratio was measured by ^1H -NMR spectroscopy. The signal centered at 1.10 ppm corresponds to the methyl group of the PO unit (d, Figure 4), whereas the signals between 3.10 and 3.60 ppm are from the protons of the methyne and methylene groups of the EO and PO units (e, Figure 4). The determination of the molar ratio was useful for the present study, because it indicated the polarity of the copolymer, with an increasing ratio of EO/PO, corresponding to an increase in polarity.

In copolymer **9**, the EO/PO ratio corresponded to the values from the supplier, while the measured EO/PO ratios in copolymers **7** and **8** were lower than the values given by the supplier (0.11 and 0.14 as compared with 0.11 and 0.21, respectively, Table 1). The measured values were used as the basis for the discussions in the present work.

Table 1. Composition of the molar ratio of ethylene oxide (EO) and propylene oxide (PO) in copolymers 7–9, as indicated from the supplier and measured by $^1\text{H-NMR}$ spectroscopy.

Copolymer	Jeffamine [®]	From supplier			Measured by NMR		
		n EO	n PO	EO/PO	n EO	n PO	EO/PO
7	M600	1	9	0.11	1	9	0.11
8	M2005	6	29	0.21	6	42	0.14
9	M2070	31	10	3.10	36	10	3.60

Copolymers 7–9 were grafted onto 6 by reaction in acetone at 50 °C. A constant grafting rate of 10 mol % was chosen to modify the polarity of copolymers 10–12 with the different Jeffamine[®] 7–9 (Scheme 2). After purification, SEC showed one population, and an increase in molecular weight as compared with 6 was observed. The measured increase was in agreement with the expected structures (Table 2). The presence of peaks at 2972 and 2876 cm^{-1} (corresponding to the C–H stretch of the CH and CH_2 groups) and at 1583 and 1540 cm^{-1} (from the CO of the amide group) in the IR spectra of 7–9 confirmed the addition of the amino group to the copolymers on 6. The successful modification of 6 was also confirmed by $^1\text{H-NMR}$ spectroscopy. The amount of grafting was determined from integration of the signals centered at 7.20 ppm of 6 (a, 5 H, Figure 4) and the signals at 1.11 and 3.60 ppm from copolymers 7–9 (e and d, 3 H, Figure 4). The reaction was found to be complete under the present reaction conditions.

Scheme 2. Preparation of copolymers 10–12 in acetone.

The grafting of 4 onto copolymers 6 and 10–12 was also carried out by reaction in acetone at 50°C. Taking the molar ratio of compounds 4 and 5 (1.2:1) into account, the amount of the mixture added to the reaction was chosen to correspond to a stoichiometric amount of 4. A complete conversion was obtained (Scheme 3). The presence of δ -damascone in copolymers 13–16 was confirmed by $^1\text{H-NMR}$ spectroscopy, where signals at 0.9 (f), 3.47 (g), 5.46 and 5.54 ppm (h, Figure 4) were observed. Integration of the signals at 5.46 and 5.54 ppm from the double bond of 4 (h, 2 H, Figure 4) and the signals at 7.20 ppm from the styrene units (a, 5 H, Figure 4) confirmed the complete conversion of 4.

In addition, IR spectra showed not only the absence of peaks at 1773 and 1854 cm^{-1} of the maleic anhydride in copolymers **6** and **10–12**, but also the presence of new peaks at 3020 and 1702 cm^{-1} (Figure 5), which were previously observed in **4**. Finally, an increase in molecular weight was measured by SEC (Table 2).

Scheme 3. Preparation of δ -damascone-releasing bioconjugates **13–16**.

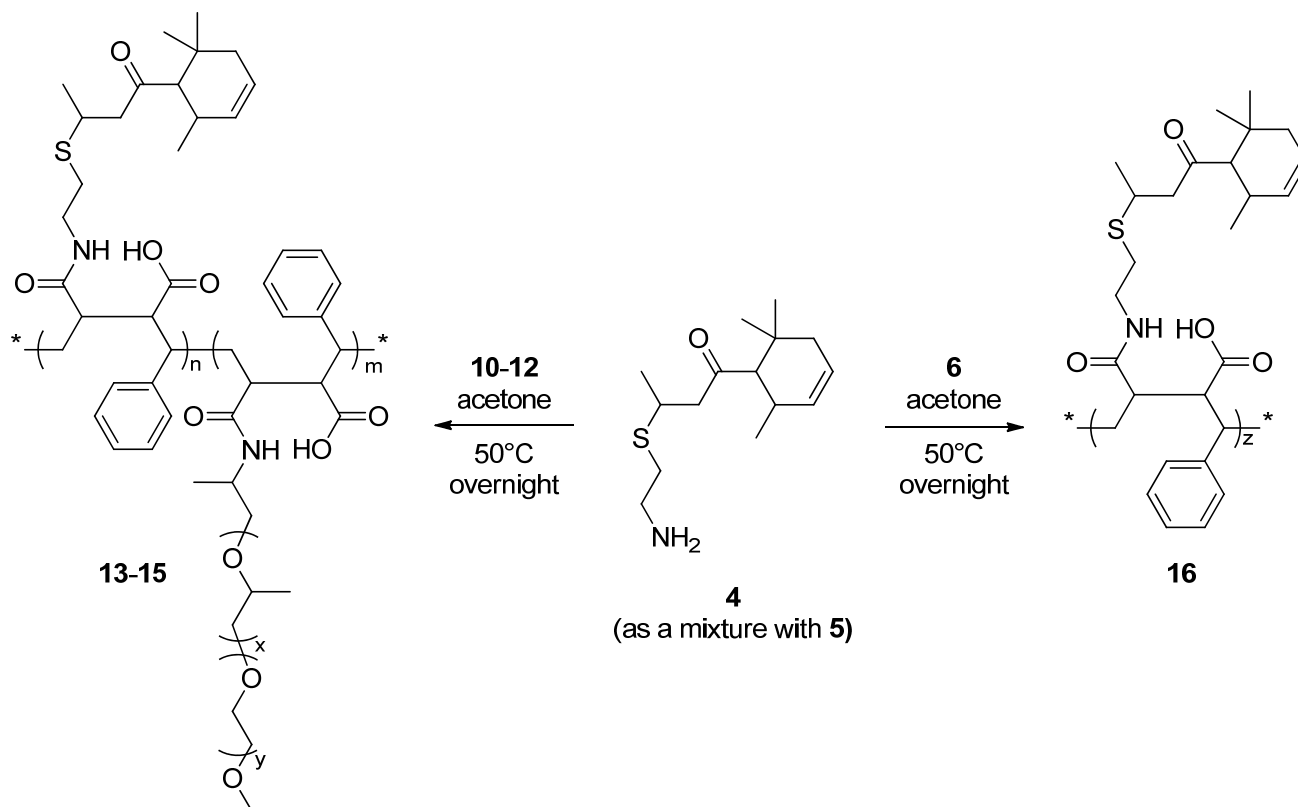


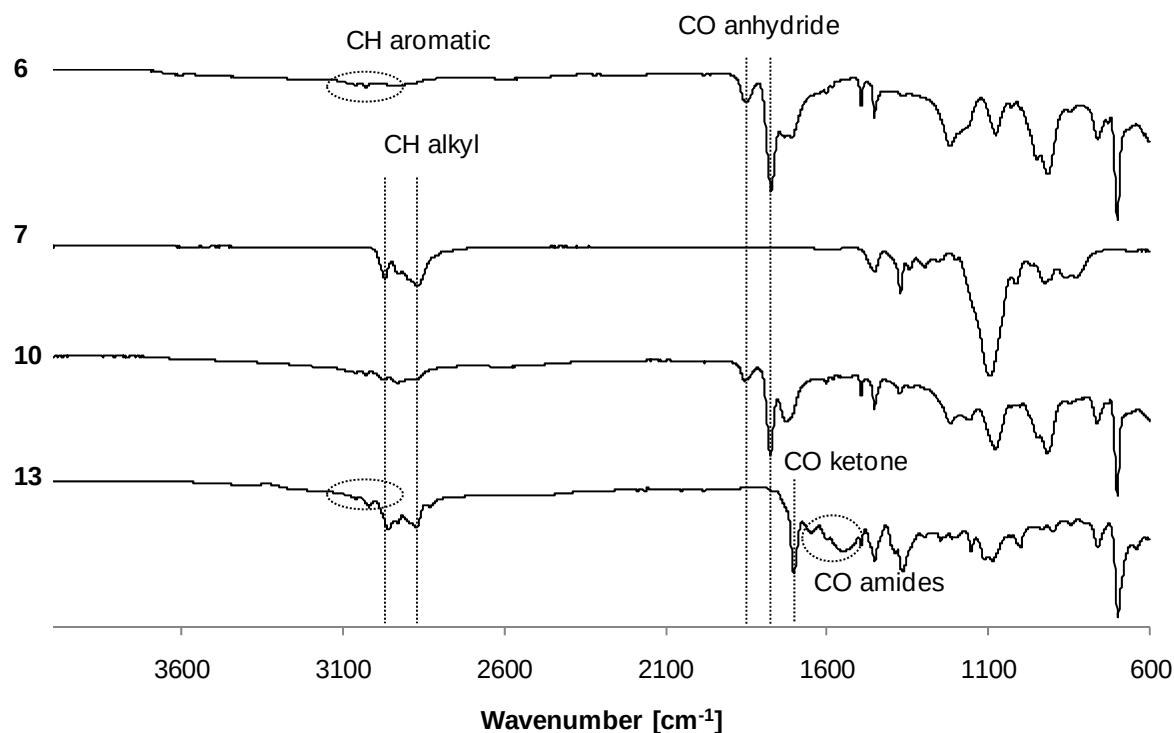
Table 2. Number average (M_n) and weight average (M_w) molecular weights and polydispersity indices (PDIs) of copolymers **6** and **10–16** measured by size-exclusion chromatography (SEC) in tetrahydrofuran (THF) using poly(styrene) as the calibration standard.

Copolymer	M_n	M_w	PDI	Copolymer	M_n	M_w	PDI
6	2100	2800	1.33	13	3100	5800	1.87
10	2600	4800	1.85	14	3900	9000	2.31
11	3600	7600	2.11	15	3500	7000	2.00
12	3560	6300	1.77	16	3200	7100	2.22

The loading of δ -damascone in conjugates **13–16** was determined by ^1H -NMR spectroscopy (Table 3). The loading varied between 25.6 wt % in copolymers **14** and **15**, 32.3 wt % in **13** and 38.3 wt % in **16**.

Table 3. Loading of δ -damascone in conjugates **13–16** as determined by ^1H -NMR spectroscopy.

Copolymer	wt % δ -damascone
13	32.3
14	25.6
15	25.6
16	38.3

Figure 5. Fourier transform infrared spectroscopy (FTIR) spectra of copolymers **6**, **7**, **10** and **13**.

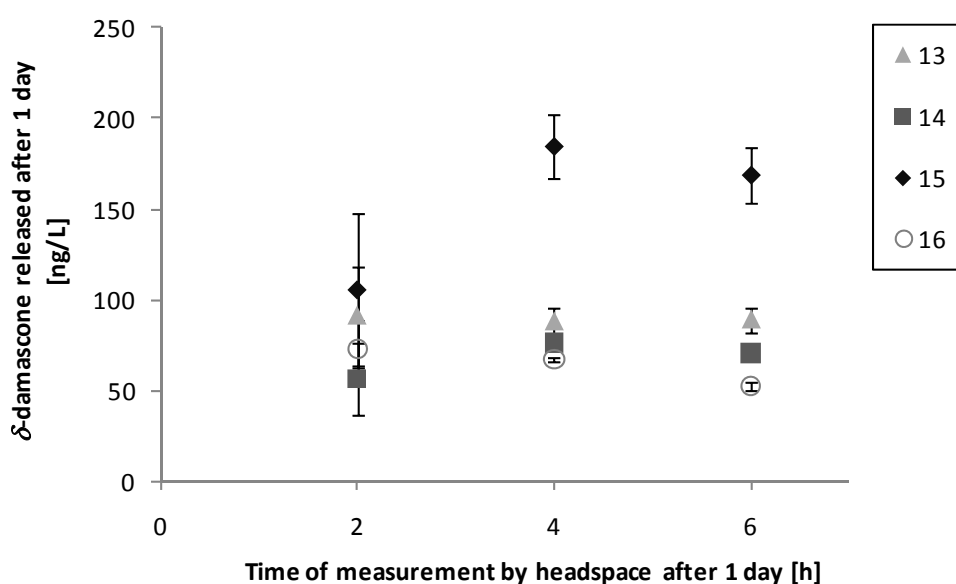
3.3. Performance on Fabric

The influence of the structure of the grafted poly(ethylene oxide)-poly(propylene oxide) (PEO-PPO) copolymers on the release of δ -damascone was investigated by dynamic headspace analysis [38,39] of the volatile molecule from a cotton surface after application of a fabric softener solution. Typical fabric softener formulations consist of about 15% of a cationic surfactant, such as triethanolamine (TEA)-esterquats of fatty acids [40,41], in water. For the measurements, conjugates **13–16** were dissolved in ethyl acetate at a concentration to potentially release a total of 8.7 mg (0.05 mmol) of δ -damascone. The solutions were then dispersed in 5.0 g of a TEA-esterquat fabric softening formulation consisting of an emulsion of cationic surfactant at 16.5% in water. The samples were constantly stirred to obtain homogeneous dispersions. The different fabric softener dispersions (1.8 g) were dissolved with water (600 mL), which corresponds to the water added to a fabric softener in a washing machine. To this diluted aqueous emulsion, a cotton sheet was added and stirred for 3 min to simulate the deposition of fabric softener and then left standing for another 2 min in the

dispersion. The cotton sheet was then wrung out and weighed to leave 3.9 g of the dispersion on the sheet. The cotton sheet was finally line dried at room temperature for 1 day [27].

The cotton sheet was then placed inside a headspace sampling cell and exposed to a constant flow of air to constantly remove the volatiles evaporating from the cotton surface. The δ -damascone released from copolymers **13–16** was collected at constant time intervals on a Tenax[®] cartridge and then analyzed by gas chromatography after thermal desorption [27]. Three measurements were taken, one each after 2, 4 and 6 h of sampling. The data illustrated in Figure 6 are average values of at least two measurements.

Figure 6. Headspace analysis of copolymers **13–16** as a function of time, measured after 24 h of line drying.



The water content of the polymers has been neglected in the current study because the polymers were formulated in an aqueous environment for the application. Furthermore, the headspace sampling was carried out with constant humidity in the air. We therefore assume that the water activity was constant for all measurements. Dynamic scanning calorimetry measurements carried out on the pure polymers between -25 and 110 °C (to represent realistic application conditions) did not show phase transitions. This indicated that residual water did not have an influence on the release kinetics.

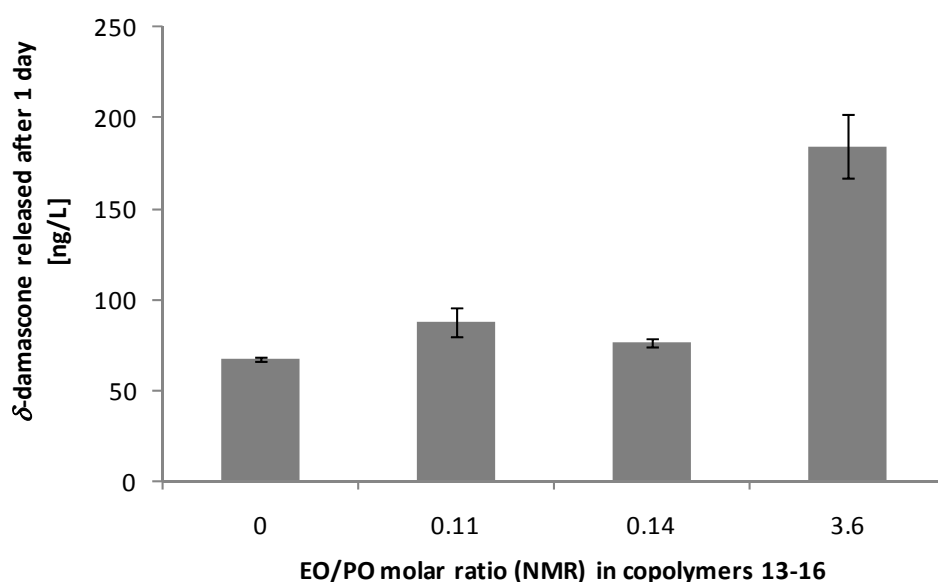
After 2 h of sampling, headspace concentrations with relatively large standard deviations were measured, whereas relatively low standard deviations were obtained for the data acquired after 4 and 6 h of sampling. This suggests that the deviations observed at the beginning of the measurements are not the result of uncontrolled deposition of the conjugates on the cotton surface, but rather because an initial amount of time is necessary to equilibrate the headspace system before reaching a state in which headspace concentrations can be collected with good reproducibility. This phenomenon has been observed previously in a similar context [42,43]. Under the present reaction conditions, the highest headspace concentrations were measured after 4 h.

The headspace concentrations of δ -damascone released from conjugate **16** were found to be the lowest of the series, with 67 and 53 ng L^{-1} , measured after 4 and 6 h, respectively. These concentrations increased slightly for the release from conjugates **13** and **14**, where 88 and 76 ng L^{-1}

were recorded after 4 h. The highest headspace concentrations of δ -damascone were measured above the sample of conjugate **15**, with a value of 184 ng L^{-1} after 4 h (Figure 6).

Figure 7 compares the performance of δ -damascone conjugates **13–16** by plotting the headspace concentrations measured after 4 h as a function of the EO/PO molar ratio in the Jeffamine[®] side chain. Conjugate **13**, with an EO/PO ratio of 0.11, gave rise to slightly higher headspace concentrations of δ -damascone (88 ng L^{-1}) than conjugate **16** (67 ng L^{-1}), which has no EO/PO side chains. Conjugate **14**, with an EO/PO ratio of 0.14 in the side chain, gave rise to 76 ng L^{-1} of δ -damascone above the dry cotton surface. As a consequence, the grafting of PPO or of copolymers with a low EO/PO molar ratio did not improve the performance of the profragrances in the targeted application.

Figure 7. Headspace concentrations of δ -damascone on dry cotton as a function of EO/PO molar ratio in the side chain of conjugates **13–16** after line drying for 24 h and sampling for 4 h.



However, grafting of a side chain with a high EO/PO ratio significantly improved the amount of δ -damascone released into the headspace. Moving from δ -damascone conjugate **16** (with no EO/PO side chains) to copolymer **15** (with a EO/PO ratio of 3.60 in the side chains) increased the amount of δ -damascone in the headspace from 67 to 184 ng L^{-1} , corresponding to an increase by a factor of more than three (Figure 7). This result was somehow unexpected. In our previous work, the grafting of a PEO side chain onto a δ -damascone-releasing poly(maleic anhydride) profragrance derived from **3** (Figure 2) resulted in a decrease in performance on dry cotton [27]. Although the presence of the polar PEG side chain increased the performance of the delivery system in water, it was less efficiently deposited onto the cotton surface, which resulted in lower headspace concentrations in the final application.

Our present data show that increasing the EO/PO molar ratio in the polymer side chain resulted in an increase of the headspace concentration of δ -damascone evaporated from the cotton surface. This suggests that the presence of PPO in the side chain has a positive effect in improving the performance of the delivery system. It seems that the side chain with an EO/PO ratio of 3.60 represents a good balance to be sufficiently hydrophilic to efficiently increase the release of δ -damascone from the

conjugate, while the presence of PPO results in a certain hydrophobicity, which is useful for deposition on cotton. An EO/PO molar ratio is therefore suitable to achieve satisfactory deposition with sufficiently fast release kinetics.

4. Conclusions

Poly(maleic anhydride)s are interesting starting materials to access a broad range of chemical delivery systems for the release of drugs or volatile bioactive molecules. The structure of the bioconjugates can easily be modulated by ring opening of the anhydride moiety, thus allowing the grafting of different comonomers with variable polarities onto the polymer backbone. We have seen that the structure of the comonomer in the backbone of alternating copolymer of maleic anhydride is an important parameter, which can strongly influence the release kinetics of the biomolecule, as well as the deposition of the delivery system on different substrates.

In the present work, poly(styrene-*co*-maleic anhydride) was modified with Jeffamine[®] to give rise to EO/PO side chains with different molar ratios and then further functionalized with a β -mercapto ketone of δ -damascone as the fragrance-releasing unit. The different copolymer conjugates were obtained in a two-step procedure with excellent yields and complete conversions.

The release of δ -damascone from the copolymer conjugates by retro 1,4-addition was investigated by dynamic headspace analysis after deposition onto a cotton surface in the presence of a cationic surfactant. The presence of side chains with a low EO/PO molar ratio did not significantly increase the rate of δ -damascone release in the desired application as compared to the corresponding poly(styrene-*co*-maleic anhydride) without Jeffamine[®] side chains.

An efficient release of δ -damascone in the application was achieved with copolymers having a high EO/PO ratio in their grafted side chains. The presence of low amounts of PPO improved the overall performance of the present delivery system with respect to previously described materials with pure PEO side chains [27]. Our data suggest that the present copolymer conjugates represent a suitable balance of hydrophilicity and hydrophobicity of the polymer backbone to favor the release of the δ -damascone in a rather polar environment, at the same time being sufficiently apolar to improve the deposition of the conjugate from an aqueous environment onto a cotton surface. Our data thus show that the suitable structural modification of a polymer backbone with an appropriate material can strongly influence the performance of a bioconjugate in terms of release. This concept should easily be adaptable to other delivery systems and, thus, better control the release of bioactive compounds in different biomedical applications.

References

1. Ohloff, G.; Pickenhagen, W.; Kraft, P. *Scent and Chemistry: The Molecular World of Odors*; Wiley-VCH: Weinheim, Germany, 2011.
2. Herrmann, A. *The Chemistry and Biology of Volatiles*; John Wiley & Sons: Chichester, UK, 2010.
3. Berger, R.G. *Flavours and Fragrances—Chemistry, Bioprocessing and Sustainability*; Springer-Verlag: Berlin, Germany, 2007.
4. Sell, C. *The Chemistry of Fragrances—From Perfumer to Consumer*, 2nd ed.; Royal Society of Chemistry: Cambridge, UK, 2006.

5. Surburg, H.; Panten, J. *Common Fragrance and Flavor Materials: Preparation, Properties and Uses*, 5th ed.; Wiley-VCH: Weinheim, Germany, 2006.
6. Friberg, S.E. Fragrance compounds and amphiphilic association structures. *Adv. Colloid Interface Sci.* **1998**, *75*, 181–214.
7. Zhang, Z.; Friberg, S.E.; Aikens, P.A. Change of amphiphilic association structures during evaporation from emulsions in surfactant-fragrance-water systems. *Int. J. Cosmet. Sci.* **2000**, *22*, 181–199.
8. Milotic, D. The impact of fragrance on consumer choice. *J. Consum. Behav.* **2003**, *3*, 179–191.
9. Herrmann, A. Controlled release of volatiles under mild reaction conditions: From nature to everyday products. *Angew. Chem. Int. Ed.* **2007**, *46*, 5836–5863.
10. Herrmann, A. Profragrances and properfumes. In *The Chemistry and Biology of Volatiles*; John Wiley & Sons: Chichester, UK, 2010; pp. 333–362.
11. Perry, R.J. “Pro-fragrant” silicone delivery polymers. In *Delivery System Handbook for Personal Care and Cosmetic Products: Technology, Applications, and Formulations*; Rosen, M.R., Ed.; William Andrew Publishing: Norwich, UK, 2005; pp. 667–682.
12. Herrmann, A. Using photolabile protecting groups for the controlled release of bioactive volatiles. *Photochem. Photobiol. Sci.* **2012**, *11*, 446–459.
13. Derrer, S.; Flachsmann, F.; Plessis, C.; Stang, M. Applied photochemistry—Light controlled perfume release. *Chimia* **2007**, *61*, 665–669.
14. Schilling, B.; Kaiser, R.; Natsch, A.; Gautschi, M. Investigation of odors in the fragrance industry. *Chemoecology* **2010**, *20*, 135–147.
15. Rataj, V.; Ruyffelaere, F.; Aubry, J.-M. Libération contrôlée de molécules de parfum à partir de précurseurs. *Cah. Formul.* **2005**, *12*, 82–96.
16. Kamogawa, H.; Mukai, H.; Nakajima, Y.; Nanasawa, M. Chemical release control—Schiff bases of perfume aldehydes and aminostyrenes. *J. Polym. Sci. Polym. Chem. Ed.* **1982**, *20*, 3121–3129.
17. Kamogawa, H.; Haramoto, Y.; Misaka, Y.; Asada, Y.; Ohno, Y.; Nanasawa, M. Chemical release control: sulfonate esters from perfume and herbicide alcohols and p-styrenesulfonyl chloride. *J. Polym. Sci. Polym. Chem. Ed.* **1985**, *23*, 1517–1526.
18. Galioğlu, O.; Akar, A. Perfume alcohols supported to sulfochlorinated poly(styrene-co-divinyl benzene) beads. *J. Polym. Sci. A Polym. Chem.* **1988**, *26*, 2355–2357.
19. Kamogawa, H.; Kohno, H.; Kitagawa, R. Chemical release control: carbamates of 3-vinylphenyl and 2-methacryloyloxyethyl isocyanates and perfume and herbicide alcohols. *J. Polym. Sci. A Polym. Chem.* **1989**, *27*, 487–495.
20. Berthier, D.; Trachsel, A.; Fehr, C.; Ouali, L.; Herrmann, A. Amphiphilic polymethacrylate- and polystyrene-based chemical delivery systems for damascones. *Helv. Chim. Acta* **2005**, *88*, 3089–3108.
21. Trachsel, A.; de Saint Laumer, J.-Y.; Haeffliger, O.P.; Herrmann, A. Parameters influencing the release of tertiary alcohols from the surface of “spherical” dendrimers and “linear” stylomers by neighbouring-group-assisted hydrolysis of 2-carbamoylbenzoates. *Chem. Eur. J.* **2009**, *15*, 2846–2860.

22. Aulenta, F.; Drew, M.G.B.; Foster, A.; Hayes, W.; Rannard, S.; Thornwaite, D.W.; Youngs, T.G.A. Fragrance release from the surface of branched poly(amide)s. *Molecules* **2005**, *10*, 81–97.
23. Morinaga, H.; Morikawa, H.; Wang, Y.; Sudo, A.; Endo, T. Amphiphilic copolymer having acid-labile acetal in the side chain as a hydrotrope: controlled release of aldehyde by thermoresponsive aggregation-dissociation of polymer micelles. *Macromolecules* **2009**, *42*, 2229–2235.
24. Morinaga, H.; Morikawa, H.; Sudo, A.; Endo, T. Design of controlled releasing system: synthesis of an amphiphilic copolymer endowed with acid-labile side chains based on quaternarization of amine-containing prepolymer with benzyl halide having acetal moiety. *J. Polym. Sci. A Polym. Chem.* **2009**, *47*, 3241–3247.
25. Wang, Y.; Morinaga, H.; Sudo, A.; Endo, T. Synthesis of amphiphilic polyacetal by polycondensation of aldehyde and polyethylene glycol as an acid-labile polymer for controlled release of aldehyde. *J. Polym. Sci. A Polym. Chem.* **2011**, *49*, 596–602.
26. Wang, Y.; Morinaga, H.; Sudo, A.; Endo, T. Synthesis of amphiphilic copolymer having acid-labile bicyclo bisoxazolidine in the side-chain for controlled release of fragrance aldehyde. *J. Polym. Sci. A Polym. Chem.* **2011**, *49*, 1881–1886.
27. Berthier, D.; Paret, N.; Trachsel, A.; Herrmann, A. Influence of the backbone structure on the release of bioactive volatiles from maleic acid-based polymer conjugates. *Bioconjug. Chem.* **2010**, *21*, 2000–2012.
28. Tree-udom, T.; Wanichwecharungruang, S.P.; Seemork, J.; Arayachukeat, S. Fragrant chitosan nanospheres: Controlled release systems with physical and chemical barriers. *Carbohydr. Polym.* **2011**, *86*, 1602–1609.
29. Fehr, C.; Galindo, J. Aldols by Michael addition: Application of the retro-Michael addition to the slow release of enones. *Helv. Chim. Acta* **2005**, *88*, 3128–3136.
30. Kastner, D. 25 Jahre Rosenketone—Thema mit Variationen. *Parfuem. Kosmet.* **1994**, *75*, 170–181.
31. Williams, A. Rose ketones: Celebrating 30 years of success. *Perfum. Flavorist* **2002**, *27*, 18–32.
32. Saito, Y.; Miura, K.; Tokuoka, Y.; Kondo, Y.; Abe, M.; Sato, T. Volatility and solubilization of synthetic fragrances by Pluronic[®] P-85. *J. Dispers. Sci. Technol.* **1996**, *17*, 567–576.
33. Suzuki, K.; Saito, Y.; Tokuoka, Y.; Abe, M.; Sato, T. Poly(ethylene oxide)/poly(propylene oxide)/poly(ethylene oxide) triblock copolymer as a sustained-release carrier for perfume compounds. *J. Am. Oil Chem. Soc.* **1997**, *74*, 55–59.
34. Vauthey, S.; Leser, M.E.; Garti, N.; Watzke, H.J. Solubilization of hydrophilic compounds in copolymer aggregates. *J. Colloid Interface Sci.* **2000**, *225*, 16–24.
35. Kayali, I. Solubilization of fragrance compounds in block copolymer/water system. *Jordan. J. Appl. Sci.* **2003**, *5*, 42–49.
36. Berthier, D.L.; Schmidt, I.; Fieber, W.; Schatz, C.; Furrer, A.; Wong, K.; Lecommandoux, S. Controlled release of volatile fragrance molecules from PEO-*b*-PPO-*b*-PEO block copolymer micelles in ethanol-water mixtures. *Langmuir* **2010**, *26*, 7953–7961.
37. Berthier, D.; Herrmann, A. Polymer conjugates for a controlled release of active molecules. WO Patent 2008/044178, 17 April 2008.

38. Rouseff, R.L.; Cadwallader, K.R. *Headspace Analysis of Foods and Flavors: Theory and Practice*; Kluwer Academic/Plenum Publishers: New York, NY, USA, 2001.
39. Rubiolo, P.; Sgorbini, B.; Liberto, E.; Cordero, C.; Bicchi, C. Analysis of the plant volatile fraction. In *The Chemistry and Biology of Volatiles*; Herrmann, A., Ed.; John Wiley & Sons: Chichester, UK, 2010; pp. 49–93.
40. Levinson, M.I. Rinse-added fabric softener technology at the close of the twentieth century. *J. Surfactants Deterg.* **1999**, *2*, 223–235.
41. Mishra, S.; Tyagi, V.K. Ester quats: The novel class of cationic fabric softeners. *J. Oleo Sci.* **2007**, *56*, 269–276.
42. Levrand, B.; Fieber, W.; Lehn, J.-M.; Herrmann, A. Controlled release of volatile aldehydes and ketones from dynamic mixtures generated by reversible hydrazone formation. *Helv. Chim. Acta* **2007**, *90*, 2281–2314.
43. Buchs, B.; Godin, G.; Trachsel, A.; de Saint-Laumer, J.-Y.; Lehn, J.-M.; Herrmann, A. Reversible aminal formation: Controlling the evaporation of bioactive volatiles by dynamic combinatorial/covalent chemistry. *Eur. J. Org. Chem.* **2011**, 681–695.

© 2013 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/3.0/>).