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Pro-fragrances

Controlled Release of Volatiles under Mild Reaction Conditions: From Nature to Everyday Products

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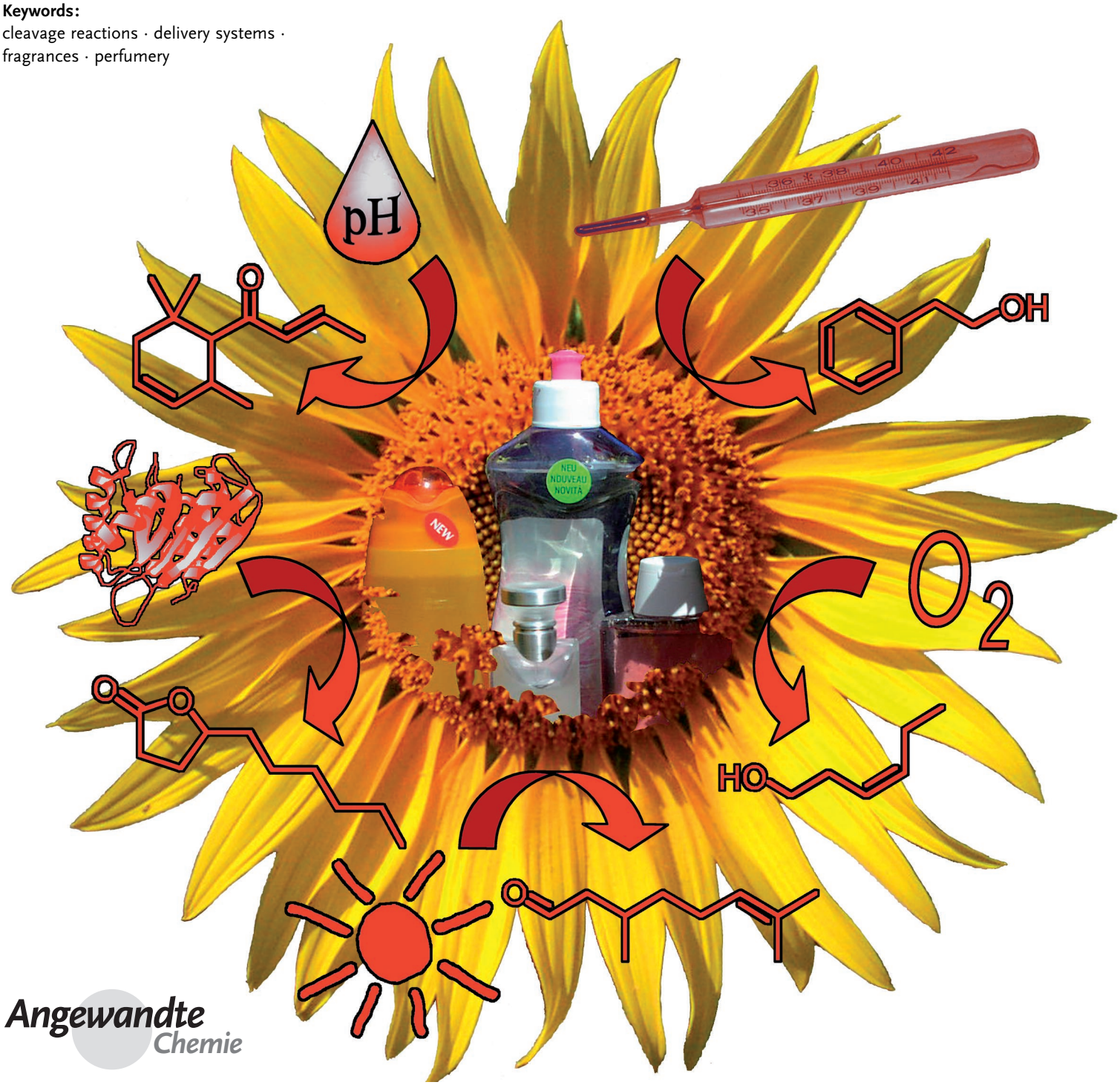

Volatile organic compounds serve in nature as semiochemicals for communication between species, and are often used as flavors and fragrances in our everyday life. The quite limited longevity of olfactive perception has led to the development of pro-perfumes or pro-fragrances—ideally nonvolatile and odorless fragrance precursors which release the active volatiles by bond cleavage. Only a limited amount of reaction conditions, such as hydrolysis, temperature changes, as well as the action of light, oxygen, enzymes, or microorganisms, can be used to liberate the many different chemical functionalities. This Review describes the controlled chemical release of fragrances and discusses additional challenges such as precursor stability during product storage as well as some aspects concerning toxicity and biodegradability. As the same systems can be applied in different areas of research, the scope of this Review covers fragrance delivery as well as the controlled release of volatiles in general.

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1. Introduction

1.1. General Aspects

Volatile organic molecules are responsible for communication between species such as plants, insects, and even mammals, and are thus of interest for both chemists and biologists.[1–3] In contrast to many other bioactive substances, for example, most pharmaceuticals, these so-called semiochemicals, infochemicals, or signaling compounds have to be emitted into the air to develop their biological activity. They are therefore generally characterized by a relatively low molecular weight which allows for an efficient evaporation, but limits at the same time the longevity of the molecule's diffusion in the air, which they require to efficiently reach their target. Nature has generated a multitude of mechanisms to store, transfer, and deliver a broad variety of semiochemicals with particular functional groups to enable and/or facilitate the everyday life of the respective species. Flowers (or plants in general) emit volatiles to attract pollinators or to protect themselves against herbivore activity.[4] The released substances mainly comprise terpenoids,[5] fatty acid derivatives (including aldehydes, esters, or alcohols), benzenoids as well as a series of nitrogen- and sulfur-containing compounds.[4,6,7] They are formed or transformed by the plant from precursors such as fatty or amino acids, carotenoids, and glycosides in biochemical pathways by specific enzymes. The substances are released into the atmosphere at rates depending on the biochemical pathway itself, but also on environmental factors such as temperature, humidity, and ambient light intensity.[6] Despite their low olfactive thresholds,[8] many of these volatiles are nevertheless easily recognized by humans, even at very low concentrations. They can be identified and distinguished by their particular odors and constitute an important part of our everyday life as flavors and fragrances.

The pleasantness of the smell of flowers and spices as well as many other natural products has attracted humans over the ages. Our ancestors in ancient Egypt and Greece developed the first methods to extract odorants from different natural sources. These odorants acted as highly valuable materials for the creation of the first fine fragrances. Besides volatile organic molecules isolated from plants and other natural sources, modern synthetic organic chemistry has considerably enlarged the number of compounds that are now available to the perfumer.[9] Perfumes are generally complex mixtures of a broad variety of natural or synthetic fragrance raw materials[10] with a multitude of chemical functional groups such as alcohols, aldehydes, ketones, esters, lactones, ethers, and nitriles.[11] Fragrance molecules are often classified into three groups consisting of "top", "middle", and "bottom" notes, which represent different types of odors and, as the name already indicates, correlate to different volatilities of the corresponding class of compounds. Although this classification is neither rigorous nor systematic, top notes are usually the most volatile compounds which rapidly evaporate to give a fresh, floral, fruity, or green odor to a perfume, followed by the less volatile middle notes with aromatic, herbal, or spicy tonalities, and the relatively substantive, high-molecular-weight bottom notes comprising woody, amber, or musky odorants.

Although functional perfumery represents the main part of today's fragrance industry, perfumes are rarely associated with being part of everyday products such as soaps, shower gels, shampoos, deodorants, detergents, softeners, cosmetics, and creams. Nevertheless, it is often the pleasantness of the odor together with the longevity of the fragrance perception[12] that directly correlates with the performance of the

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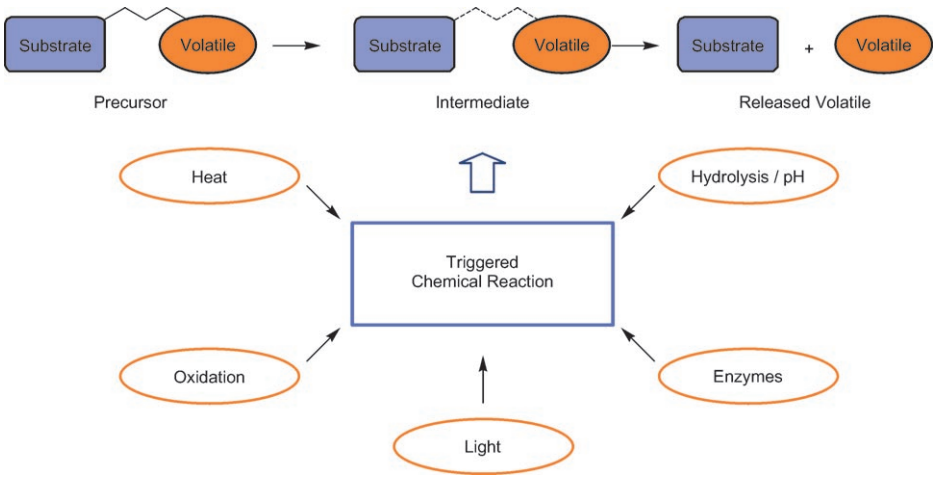
specific consumer product. The design of selective and efficient delivery systems to control the slow release of highly volatile odorants in functional perfumery products, and to increase the stability of fragrance raw materials with unstable chemical functional groups such as aldehydes, has thus become an important research area in the flavor and fragrance industry.[13–15]

Encapsulation of active compounds into matrices or specifically designed capsules is the most widely used technique to prolong the longevity of the fragrance and, as an additional benefit, to increase the stability of labile compounds in aggressive media.[13] In analogy to the release of pharmaceuticals from pro-drugs[16,17] or to the biogeneration of volatiles from plant precursors as described above, "pro-fragrances" or "pro-perfumes"[18] represent an attractive alternative to classical encapsulation techniques.[13,14] They release one or several active compounds in a chemical reaction by selective cleavage of a covalent bond of a suitably designed, usually nonvolatile and odorless precursor molecule. To perform under everyday conditions, as for example during the application of a particular consumer product, the chemical reactions involved in these processes have to involve relatively mild reaction conditions which are defined by the environment. Typical triggers that may be used for mild chemical reactions are therefore quite limited. They mainly comprise variations of temperature, exposure to (day)light, easily accessible or ubiquitous reagents such as oxygen or water (including a change in the pH value), as well as different enzymes and microorganisms (Scheme 1). Despite this limited number of "reagents", a broad variety of possible reactions has been used to generate a multitude of different volatile organic compounds. Perfume capsules and pro-fragrances or pro-perfumes are often complementary in their use because of their respective advantages and disadvantages; encapsulation systems are not discussed further in this Review.



Scheme 1. Principle of the controlled release of volatile organic molecules from pro-fragrances and possible environmental reaction conditions which trigger the cleavage of a covalent bond.

A selection of natural and synthetic fragrance chemicals together with their trivial names and olfactive descriptors[11] are illustrated in Scheme 2 as typical examples of volatiles released from pro-fragrances.[19] These compounds, many of them with fresh, floral, fruity, and green odors, are classified according to their chemical functional group, which is generated from the corresponding precursor by cleavage of a covalent bond. To facilitate their identification within the different precursor structures the fragrance moieties to be released are color-coded in the further discussion of this work (alcohols in blue, aldehydes and ketones in orange, lactones and esters in green, and others in magenta). Typical substance classes represented with some examples in Scheme 2 comprise terpenes,[5] norisoprenoids (the so-called rose ketones[20]), and aromatic aldehydes or ketones. To underline the generality of the concept for the release of bioactive volatile molecules (Scheme 2) from various precursors in other domains, those fragrance molecules which were also found to interact with insects are additionally marked with an asterisk (*).[21]

1.2. Analytical Tools

Several analytical techniques may be considered to investigate the release performance of the volatiles depicted in Scheme 2 from their respective precursors. The most straightforward approach is through evaluation by an olfactive panel, where the performance of the precursor is compared to that of the corresponding unmodified fragrance molecule. Panel evaluations can be carried out directly with the desired consumer product and do not require complex analytical methods. If a sufficient number of panelists is used, the statistical significance of the experiment can be determined. The most commonly employed method to obtain quantitative data is gas chromatography (GC), either after solvent extraction of the sample or in combination with headspace sampling.[22] Headspace techniques, which have successfully been used for the identification of volatiles

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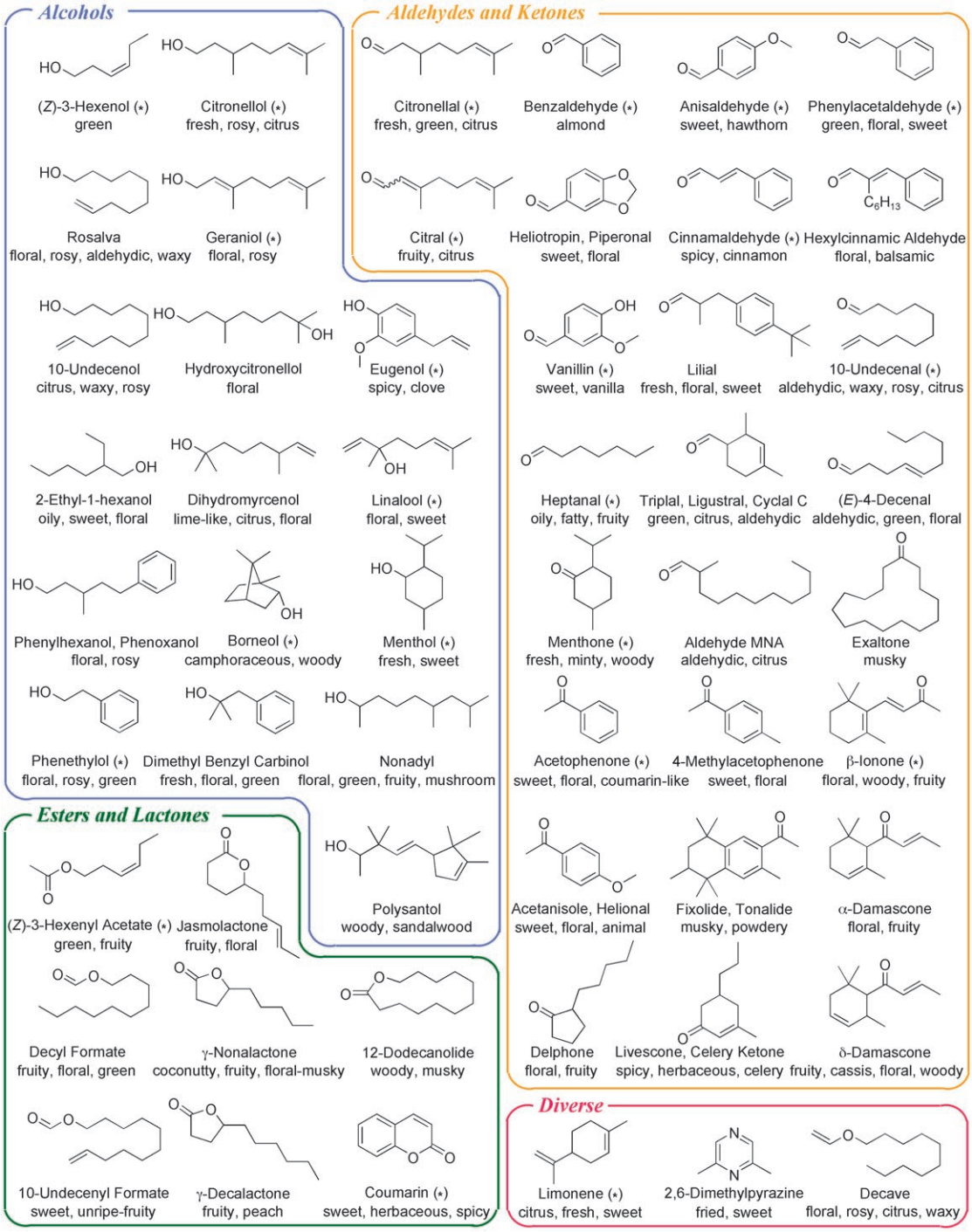


Scheme 2. Selection of volatile organic compounds that have been released from pro-fragrances.[11,19] For easy identification in the further discussion, the compounds are classified and color-coded by the functional group that is (generally) released (alcohols are marked in blue, aldehydes and ketones in orange, esters and lactones in green, and others in magenta).

emitted from plants,[23] have the advantage of generally not requiring complex sample preparation, as the volatiles are directly trapped above the sample by reversible adsorption on a polymer substrate and analyzed by GC after thermal desorption. The experiments are typically carried out in a closed container (Figure 1). Static headspace analysis, also referred to as solid-phase microextraction (SPME),[24] allows determination of the composition of the gas phase which is in equilibrium with the solid or liquid sample. In a typical set-up the polymer substrate is fixed on the top of a syringe needle, which after analysis can directly be desorbed in the injector of the gas chromatograph (Figure 1a). In dynamic headspace analysis (Figure 1b), the gas phase above the sample is continuously removed to account for the convection to which

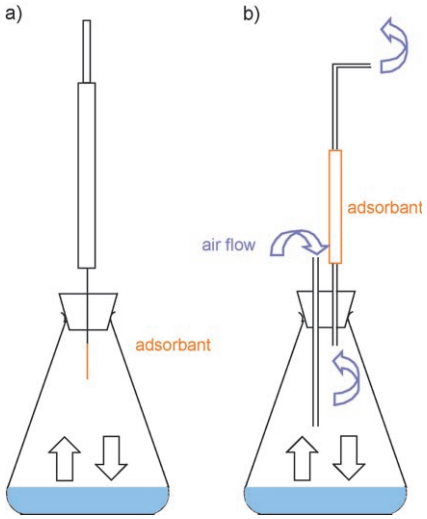


Figure 1. The principle of a) static and b) dynamic headspace sampling.

a sample is subjected when exposed to the air. This allows the evaporation kinetics of the volatiles to be monitored under non-equilibrium conditions. In a typical experiment, a constant flow of air is pumped across the sample and across a cartridge containing the polymer adsorbent. The cartridge is then subjected to thermal desorption and analyzed by GC.

1.3. Aims

The goal of this article is to focus on the mild reaction conditions which are found in everyday life and their use to release volatile organic molecules from various precursors. The synthesis of the precursors themselves, although sometimes not trivial, will not be discussed in detail, and interested readers may refer to the cited literature. The different triggers that may be used will be reviewed in a structure-based approach from the viewpoint of an organic chemist, starting with heat release systems which were historically the first class of pro-fragrances to be developed. The discussion will be followed by oxidation reactions, light-sensitive delivery systems, the use of enzymes and microorganisms, and conclude with hydrolytically labile pro-fragrances which represent up to now the largest part of the research in this area. For clarity, pro-fragrances which can release fragrances by using different types of reactions simultaneously or consecutively will be discussed with the trigger that has been identified as the most prominent. As a consequence of the strong commercial interest in these systems, most of the literature on chemical fragrance delivery systems consists of patents, and only recently has an increasing amount of work been published in the scientific literature. Although most of the literature summarized in this Review refers to the release of fragrances or semiochemicals, the concepts and applications outlined can be generalized for the design of delivery systems for other biologically active volatiles.

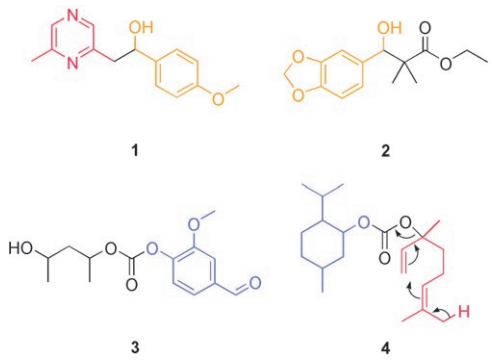
2. Temperature

Heating is the most general way to overcome the activation energy barrier for bond-forming and -breaking reactions; heat-activated delivery systems were therefore among the first pro-fragrance technologies that have been developed. Although thermolyses can not necessarily be considered as mild reactions, increased temperatures are available in numerous situations in everyday life, such as hair drying, ironing, and cooking, and may thus serve as triggers to release volatile molecules from suitably designed precursors. Whereas the temperature of the substrate usually remains below 80 °C during hair drying and ironing, higher temperatures are typically obtained in burning candles, during smoking, and in the preparation of food. Heating during cooking is a common way to generate flavor compounds from various precursors.[25] As process or reaction flavors, with the Maillard reaction being probably the most typical example, have already been extensively reviewed elsewhere,[26] they will not be further discussed here. Despite the fact that the chemicals used for many flavor and fragrance applications are identical in structure and their perception mechanism for humans is essentially the same, the registration of new synthetic and non-natural precursors is far more difficult for flavor applications than for fragrances. As a consequence, the development of pro-flavor-type technologies based on synthetic precursors is far less attractive for practical use. Nevertheless, some flavor applications, notably for tobacco products, have been reported and will be discussed here briefly using some general examples.[25]

The high volatility and ease of sublimation of flavors or flavor additives in tobacco compositions results in a decreased shelf-life of the products and thus initiated the research on pro-flavors or pro-fragrances which are cleavable by thermal activation. In 1956, Ashburn and Teague reported the preparation of polyhydroxy esters of galactose, sorbose, and poly(vinyl alcohol) for the controlled release of small carboxylic acids upon pyrolysis in tobacco preparations.[27,28] Besides carboxylic acids, which are still reasonably substantive, the development of thermolysis-based delivery systems rapidly focused on the slow release of the much more volatile alcohols or aldehydes, namely menthol, vanillin, and cinnamaldehyde as well as of pyrazines, all of which are interesting for their olfactive and gustative properties.

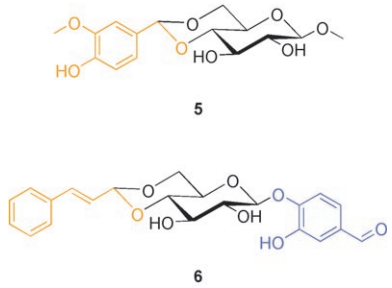
The thermal release of aryl aldehydes and/or alkyl pyrazines from 2-(2-hydroxy-2-arylethyl)pyrazines such as **1**,[29,30] β-hydroxy acids, or esters such as **2**,[31] pinacols[32] or urea compounds[33] (Scheme 3) requires rather high temperatures (> 150 °C) and was mainly reported for use in tobacco products, candles, and some specific foodstuffs. Carbonate esters of vanillin (**3**),[34,35] menthol (**4**),[36–38] and phenethylol[35] release the corresponding alcohol or phenol by pyrolysis at much lower temperatures. The thermolysis of **4** yields menthol, CO_2, and limonene (Scheme 3) as the only reaction products.[36] In some specific cases the formation of alkenes by thermal elimination of carbonates was also reported.[39]

The natural status of sugars means that there is good potential for carbohydrate conjugates and their derivatives to be accepted as food-grade compounds, thus allowing their use



Scheme 3. Heat-activated precursors for the release of aldehydes and alcohols.

as additives in flavor preparations. Upon heating, they release either alcohols or phenols through cleavage of the glycoside bond,[35,38,40,41] aldehydes from cyclic acetals (**5**),[42] or even both from mixed derivatives such as **6**[43] (Scheme 4). Pre-

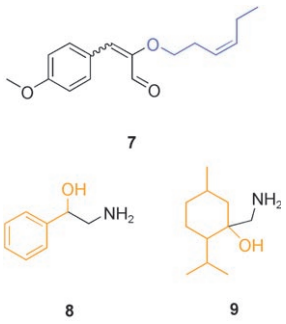


Scheme 4. Examples of thermally labile carbohydrate conjugates.

cursor **5**, for example, releases vanillin when heated to temperatures above 70 °C in the presence of humidity, and was found to be useful as a flavor additive for microwaved or cooked food, tobacco products, and for the preparation of chewing gum.[42] Carbonates,[35] glycosides, and acetals of carbohydrates[42] as well as tartrates[44,45] are also hydrolytically and/or enzymatically unstable, and can thus be used for the release of fragrances in aqueous media and/or in the presence of enzymes and microorganisms, as discussed in Sections 5 and 6.

3. Oxidation

As oxygen is responsible for the slow degradation of labile functional groups, such as aldehydes, during prolonged product storing, it may also serve as an easily accessible reagent for the slow degradation of pro-fragrances in different applications. However, its ubiquity makes it difficult to control its action on the precursor. A continuous degradation of oxygen-sensitive pro-fragrances is therefore expected, rather than a triggered, spontaneous release of the active substances in the targeted application. Thus, only a few oxidative fragrance delivery systems have been developed so far. Hashizume et al. reported the preparation of 2-alkoxy-3-arylpropenals such as **7** (Scheme 5) by condensation of an



Scheme 5. Precursors for fragrance release by oxidative bond cleavage.

aromatic aldehyde with an acetaldehyde of a fragrance alcohol.[46] The fragrance is released from paper by slow oxidation of the pro-fragrance when exposed to air, however no details of the release mechanism are given.

Aldehydes and ketones can be released by oxidation of β-amino alcohols, as reported by Reymond and co-workers.[47] Pro-fragrances **8** and **9** can be incorporated into solid inorganic supports by grinding them at 1 wt% concentration with Na_2SO_4 or MgO and sodium periodate or sodium bismuthate, the latter reagents being required to trigger the oxidation. Benzaldehyde and menthone were released when the samples were exposed to atmospheric humidity, thus giving rise to a distinct odor which was perceptible for several weeks.[47]

Other oxidation processes (for example, photooxidation) which also allow the release of aldehydes when suitable substrates are exposed to oxygen in the presence of daylight, are discussed in the following section.

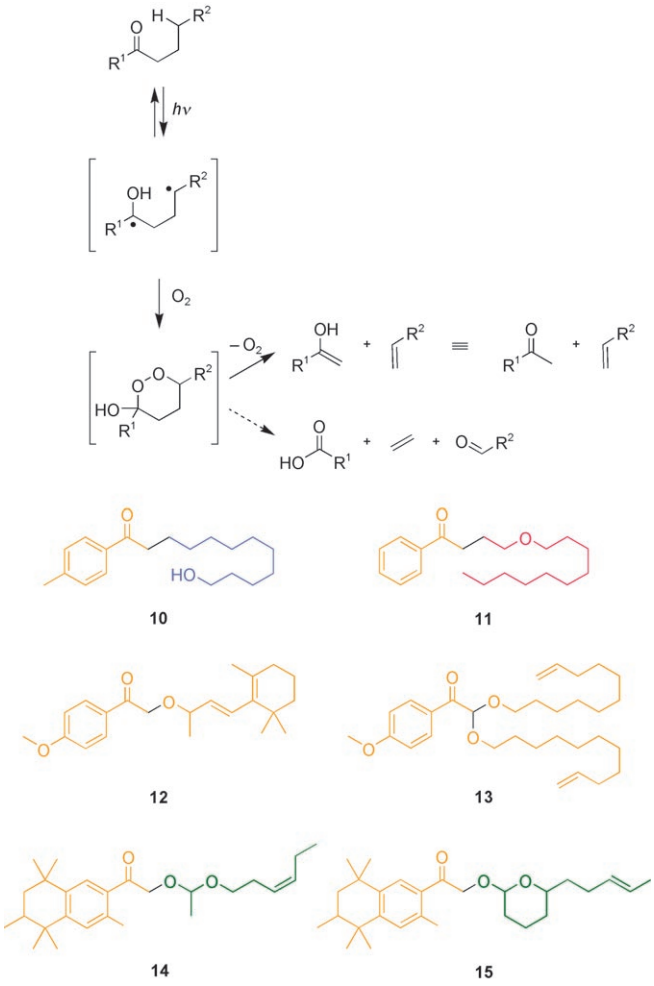
4. Light

Sunlight is one of the most important natural energy sources involved in biological processes. Light with wavelengths close to the UV region possess enough energy to generate or break covalent bonds. Photocleavable systems ("caged" compounds or ligands) have already found some application in bioorganic chemistry[48,49] and drug discovery.[50] In almost all kinds of practical applications, fragrances are deposited on various surfaces from which they slowly evaporate to be smelled. As these surfaces are generally exposed to ambient daylight, photoresponsive pro-fragrances seem to be ideal delivery systems for volatile compounds.[51,52] Furthermore, for an efficient release, they have to work in a polar environment, preferentially in water, and tolerate the presence of oxygen. Photolabile pro-fragrances are either deposited on the target surface during the use of a cleaning or surface-treatment product[51] or can be incorporated directly into surface coatings.[52]

4.1. Photofragmentations

The Norrish type II photofragmentation of carbonyl derivatives[53] is a typical example of a reaction that fulfils

these criteria.[51] The mechanism is based on an intramolecular γ-hydrogen abstraction by the oxygen atom of the carbonyl group in its excited triplet state to form a transient 1,4-biradical, followed by cleavage of the original C(α)–C(β) bond (Scheme 6). The reaction yields a carbonyl compound

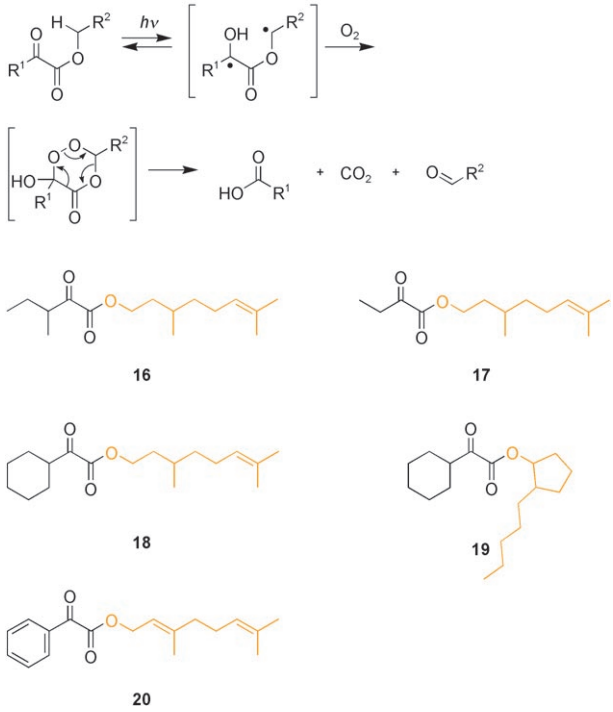


Scheme 6. Norrish type II photofragmentation of alkyl phenyl ketones and phenacyl ethers or acetals.

together with an alkene derivative,[53–55] both of which may be olfactively interesting compounds.[51] The most general group of precursors that undergo Norrish type II reactions are alkyl phenyl ketones.[55] As the photoreaction tolerates a broad variety of structural modifications in proximity to the carbonyl group as well as in the alkyl chain, it has been successfully used to generate acetophenones together with a multitude of different other fragrance molecules[51] such as alkenes and vinyl ethers from alkyl phenyl ketones (**10** and **11**),[56,57] aldehydes and ketones from phenacyl ether derivatives (**12** and **13**),[58] as well as esters and lactones from phenacyl acetals (**14** and **15**)[59] (Scheme 6).

Although the "classical" Norrish type II photoreaction depicted in Scheme 6 was found to be the predominant reaction observed for the photoirradiation around 350 nm in non-degassed solution or in different practical applications, a series of side products have been identified which arise from the presence of oxygen.[56] Photoirradiation of **11** in acetonitrile for three hours afforded 43% of acetophenone and 40% of decyl vinyl ether as the expected Norrish type II reaction products, together with 9% of decyl formate and 9% of decanol, both of which are perfumery ingredients themselves, as well as unquantified amounts of benzoic acid.[56,60] Whereas the formation of decanol remained unexplained, the release of benzoic acid and decyl formate was attributed to the rearrangement of a cyclic species which can be formed by reaction of oxygen with the intermediate 1,4-biradical (Scheme 6).[51,56]

Alkyl or aryl α-keto esters (2-oxoesters) also undergo Norrish type II reactions in the presence of oxygen to form aldehydes (or ketones) together with a carboxylic acid (Scheme 7).[51,61,62] Keto esters **16**–**20** release the corresponding aldehydes or ketones in good yields on photooxidation with a xenon lamp or outdoor sunlight.[63,64] A systematic study of the photoreaction in non-degassed solution revealed that both alkyl and ester chain fragmentations are in competition with each other. Whereas the desired fragmentation of the ester chain of **16** directly yields citronellal, fragmentation of the alkyl chain affords keto ester **17**, which then can further react by fragmentation of the ester chain to release citronellal.[64] (Cycloalkyl)oxo acetates (such as **18** and **19**) or oxo(phenyl) acetates (**20**) were found to be the most suitable pro-fragrances for the desired practical applications.[64] Dynamic headspace analysis during bodycare or household applications clearly showed an increased longevity of the fragrance release from the keto esters with respect to the corresponding unmodified reference fragrance.[63,65] Fur-



Scheme 7. Norrish type II photooxidation of α-keto esters.

thermore, photoirradiation of **18** in a film of an all-purpose cleaner on glass demonstrated the direct dependence of the fragrance release on the light intensity (Figure 2).[65] This effect was observed in general for photolabile precursors.[51,60]

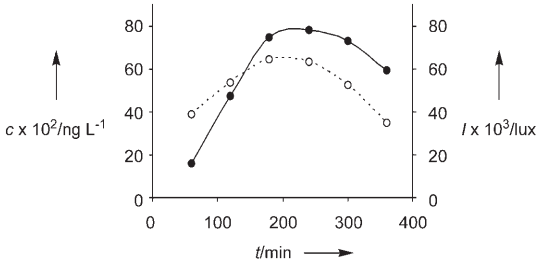


Figure 2. Dynamic headspace analysis of the light-dependent release of citronellal from precursor **18** in an all-purpose cleaning film exposed to outdoor sunlight.[65] ——: concentration of the fragrance released into the headspace; -----: evolution of the daylight intensity, with a maximum value around noon.

Photochemical reactions have been used for the deprotection of labile chemical groups in organic synthesis.[66] The protecting groups can selectively be removed by irradiation with light of a specific wavelength without interfering with other parts of the molecule. Recent developments even allow different photolabile groups in the same compound to be cleaved selectively by photolysis with light at different wavelengths.[67] In this context, compounds containing *o*-nitrobenzyl groups, originally designed for the release of carboxylic acids by photoisomerization into *o*-nitrosobenzaldehydes,[66] were structurally modified to release aldehydes upon photoirradiation at 350 nm.[68,69] Lage Robles and Bochet synthesized ether **21** (Figure 3) from the corresponding ester.[69] Photoirradiation of the pro-fragrance in non-degassed acetonitrile for three hours released (*R*)-citronellal in very good yield, as shown by ^{1}H NMR analysis.

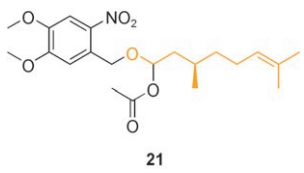


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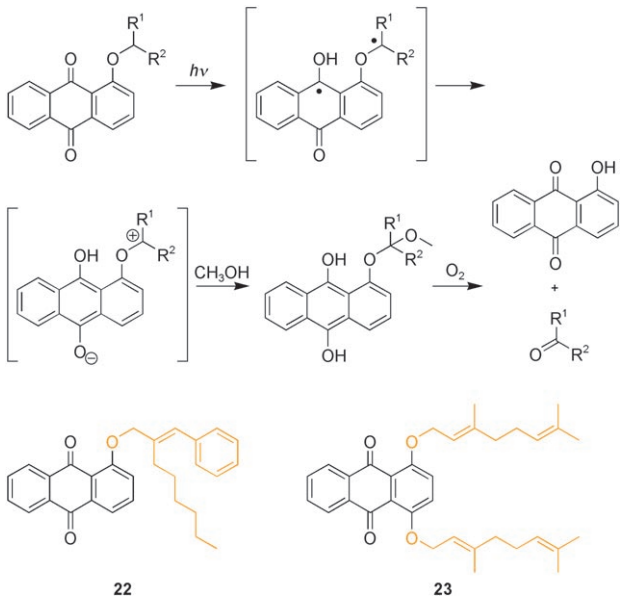
Figure 3. Photolabile ether **21** for the release of citronellal.

1-Alkoxy-9,10-anthraquinones also release aldehydes and ketones upon photoirradiation around 350 nm. The mechanism of the photoreaction is based on δ-hydrogen abstraction from the excited triplet state to form an intermediate biradical, followed by an intramolecular electron transfer to give a zwitterion. Reaction with a polar solvent (methanol) in the presence of oxygen finally yields a hydroxyanthraquinone together with a carbonyl compound (Scheme 8).[70] Pro-fragrances **22** and **23** were prepared from the fragrance bromides by reaction with the corresponding hydroxyanthraquinones.[71] Photolysis in polar and apolar solution, as well as olfactive panel evaluations on fabric after exposition to ambient indoor daylight for several days, confirmed the release of the fragrance aldehydes.



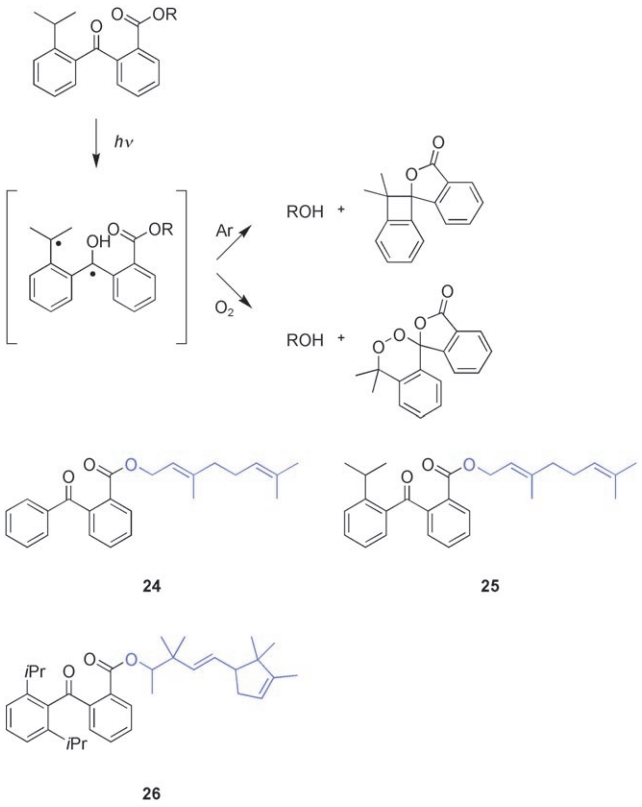
Scheme 8. Light-activated release of aldehydes from 1-alkoxy-9,10-anthraquinones.

In contrast to anthraquinone derivatives, the photoreduction of 2-benzoyl benzoates releases primary or secondary alcohols via a hydroxy radical intermediate which then eliminates the alcohol upon intramolecular cyclization (Scheme 9).[72,73] The release of geraniol from **24** requires an external hydrogen donor, such as 2-propanol, or an electron donor, such as a primary amine.[72] The introduction of an isopropyl substituent in the proximity of the carbonyl function, as for example in **25** or **26** (Scheme 9), allows the release of the corresponding fragrance alcohol independently of the reaction medium, for example, from a thin film of the corresponding compound.[63,73] Different reaction products resulting from the cyclization of the 2-benzoyl benzoate moiety were obtained in the presence or absence of oxygen.[73]

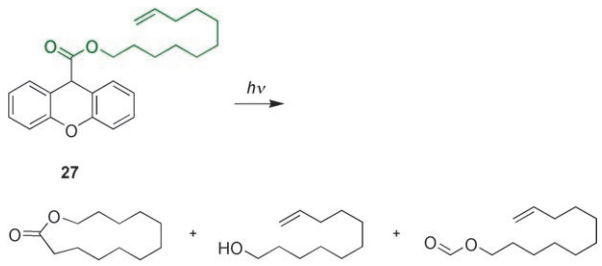
Other examples of photorelease systems for fragrances involving the cyclization of intermediate radicals were based on substituted alkoxybenzoin derivatives[74] or xanthenoic esters.[75] As reported by Plessis and Derrer, xanthenoic esters of unsaturated alcohols are homolytically cleaved to form xanthene radicals and formyl radicals upon photoirradiation above 300 nm. The latter cyclize to form lactones, the ring size of which is influenced by the location of the double bond. Photolysis of **27** (Scheme 10), for example, afforded a mixture of 12-dodecanolide together with the corresponding formyl ester and 10-undecenol.[75]

4.2. Photoisomerizations

Besides light-induced bond cleavage, indirect photorelease systems for fragrances based on a photochemical *E*/*Z* double bond isomerization of *o*-hydroxy cinnamates (*o*-



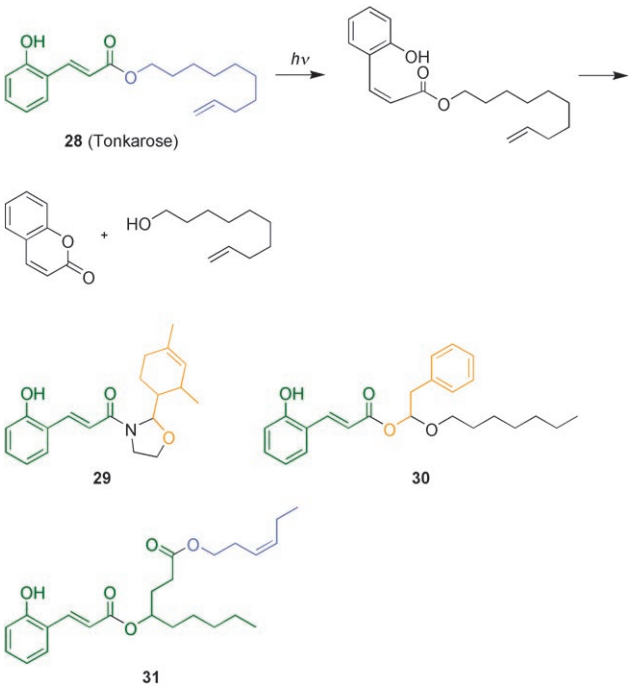
Scheme 9. Photochemical release of alcohols from 2-benzoyl benzoates in the presence or absence of oxygen.



Scheme 10. Photolactonization of xanthenoic esters.

hydroxyaryl acrylates) followed by intramolecular lactonization of the *Z* isomer have been developed (Scheme 11). The corresponding pro-perfumes release coumarin together with a fragrance alcohol in a 1:1 ratio as reported by Anderson and Fráter.[76] The photoactivated isomerization of the double bond of *o*-hydroxy cinnamates was previously developed to control the activity of thrombin and trypsin, either by the preparation of a photolabile enzyme inhibitor or by acylation of the enzyme with the photoremovable *o*-hydroxy cinnamate unit as a photocleavable enzyme conjugate.[77]

o-Hydroxy cinnamate pro-perfumes, such as **28** (Scheme 11),[76] which is commercialized under the trade name tonkarose, can be synthesized in one step by reaction of the corresponding alcoholate with coumarin.[78] The different compounds were evaluated on fabric, which was dried in the presence or absence of sunlight. Olfactive evaluation of the



Scheme 11. Photochemical release of the fragrance triggered by *E*/*Z* isomerization of the double bond of *o*-hydroxy cinnamates followed by intramolecular lactonization.

test fabric revealed a distinct fragrance note in the samples dried in sunlight, whereas the cloth dried without sunlight was found to be olfactively neutral.[76]

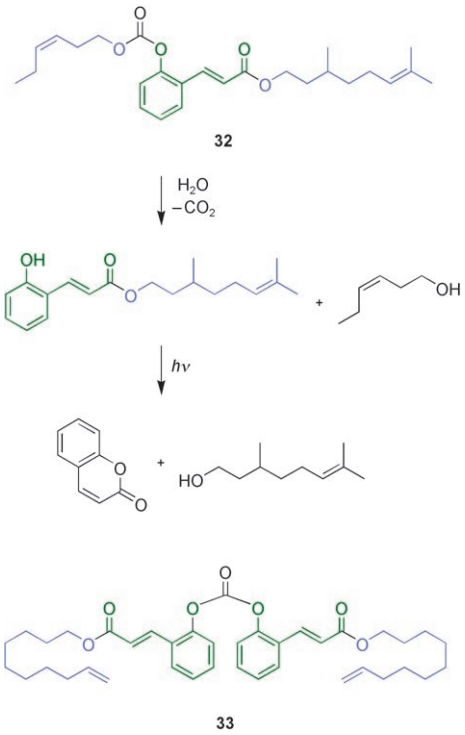
In a further development, Dykstra and Gray prepared *o*-hydroxy cinnamates for the release of tertiary alcohols,[79] as well as several multistep release systems using photoisomerization as the first step of a cascade reaction (Scheme 11).[80,81] After photoinduced lactonization, pro-perfume **29** releases coumarin and an oxazolidine derivative, which further hydrolyzes to yield a fragrance aldehyde.[80] *o*-Hydroxy cinnamate derivative **30** affords coumarin, an aldehyde, and an alcohol,[81] whereas **31** yields coumarin, a lactone, and an alcohol[82] in a similar photolactonization-initiated sequence.

Flachsmann and Bachmann proposed the protection of the phenol group as a carbonate to circumvent the problem of undesired discoloration effects in consumer products or on the substrates to which the products were applied, (Scheme 12).[78] Again the fragrance molecules are released in a cascade reaction, this time with the hydrolysis of the carbonate as the first step followed by light-induced lactonization to release coumarin and two fragrance alcohols in a 1:1:1 molar ratio (**32**) or a 1:1 mixture of coumarin and an alcohol in the case of dimer **33**.[78]

5. Enzymes and Microorganisms

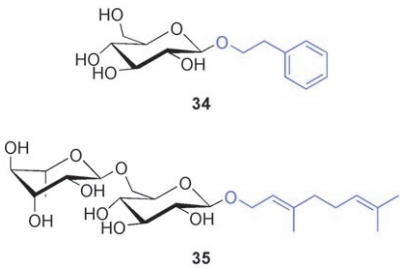
5.1. Glycosidases

Glycosidically bound volatile compounds such as mono- or sesquiterpenes, aliphatic alcohols, and a series of phenyl-



Scheme 12. Multistep release of the fragrance by a hydrolytic cleavage of a carbonate ester followed by a photoinitiated intramolecular lactonization.

propane derivatives represent an important class of precursors with a widespread occurrence in many different plant species.[83] As a consequence of their high water solubility, glycosides may be considered as transport or storage compounds for the volatile and mostly hydrophobic aglycones, which are released from the precursor by the action of glycoside hydrolases or glycoside transferases.[83] Various types of glycosidases have been identified in plants and on the skin, and also in microorganisms such as yeasts, fungi, and bacteria. Glycosidases from skin or skin bacteria can thus release a broad variety of fragrance alcohols from monosaccharides (such as glucose, galactose, mannose, and rhamnose) or disaccharides (for example, lactose, maltose, and sucrose) and are therefore useful natural precursors for the enzymatic release of insect repellents and fragrances in cosmetic or bodycare applications.[84–89] Besides the broad variety of naturally occurring glycosides,[83] derivatives of other volatiles can easily be prepared.[85,86] The evaluation of glycosides such as **34** and **35** (Scheme 13), carried out with specific enzyme preparations or bacteria cultures, confirmed the expected sustained release effect of the precursors, with respect to the unmodified reference compound, under the desired application conditions on skin or hair.[84,85] The release of phenethylol and geraniol from **34** and **35**, respectively, was followed by GC, high-performance liquid chromatography (HPLC), headspace analysis, and panel evaluations. It was shown that β-glucosides are more easily cleaved by enzymes than the corresponding α form[85] and that terpene diglycosides such as **35** are hydrolyzed in a two-step sequence.[87] The first step usually comprises the cleavage of the disaccharide

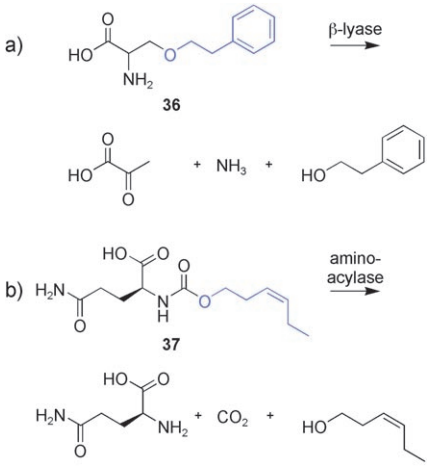


Scheme 13. Glycosidic precursors **34** and **35**.

bond and the second step the release of the terpene alcohol from the remaining monoglycoside. Depending on the nature of the sugar moieties, the two steps may be carried out by the same or by different glycosidases.

5.2. β-Lyases and Aminoacylases

Skin bacteria enzymes, in particular those of axilla bacteria, can transform odorless proteinaceous secretions into malodors.[90] Up to now, several enzymes of *Corynebacteria* or *Staphylococci*, namely pyridoxal phosphate dependent β-lyases[91] and Zn^{2+}-dependent aminoacylases,[92] have been identified that generate thiols or hexanoic acid derivatives, respectively. The knowledge of the enzymatic mechanisms in the formation of human body malodor helps in the development of new types of bodycare products and deodorants. Suitably designed fragrance precursors, which are cleaved by the malodor-creating enzyme to release neutral or pleasant odors, represent an interesting alternative to the use of antibacterial agents or enzyme inhibitors.[93] The cleavage of precursors by pyridoxal phosphate dependent amino acid β-lyases was reported to give a pyruvate, ammonia, and—depending on the substitution of the precursor—an alcohol, thiol, or carboxylic acid (Scheme 14a).[94,95] The release of phenethylol (from **36**) successfully reduced the formation of malodors from protein-

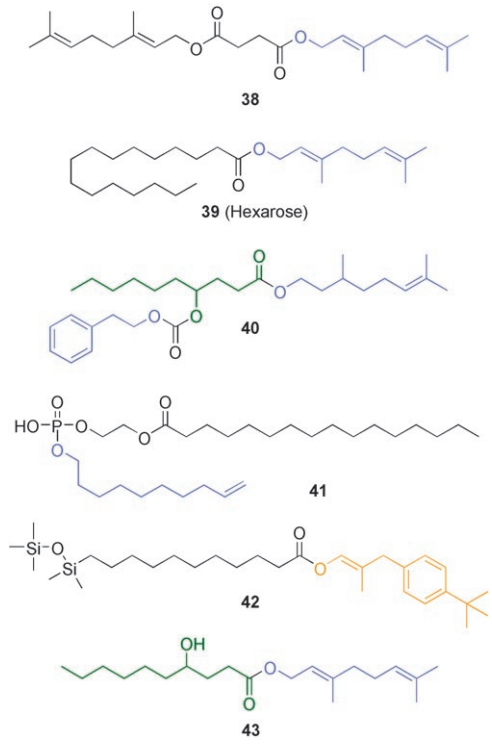


Scheme 14. Enzymatic cleavage of substrates by a) β-lyases or b) aminoacylases for the controlled release of volatile alcohols.

containing secretions in a deodorant formulation.[95] In a similar approach, Natsch et al. prepared carbamate **37** which releases, in the presence of *N*-acylglutamine aminoacylase from *Corynebacteria*, (*Z*)-3-hexenol, CO_2, and glutamine (Scheme 14b).[96] Axilla bacteria (*Staphylococcus haemolyticus*) also efficiently cleave serine carbonates, and these were therefore used as versatile precursors for the release of fragrance alcohols.[97]

5.3. Hydrolases

Hydrolases (in particular lipases) represent another important class of enzymes which are found either in the extracellular *Stratum corneum* of the skin[98] or in skin bacteria.[99] As a consequence of their ability to cleave triglycerides, specific lipases that tolerate high pH values, elevated temperatures, and the presence of surfactants, bleaches, or other cleaning ingredients have been developed as additives for stain removal in detergents.[100,101] Lipases are therefore present in many applications of functional perfumery, and have been successfully used to trigger the release of volatiles under relatively mild conditions, as found on the skin surface or on dry fabric. Various fragrance or insect-repellent alcohols have been successfully released from carboxylic esters (**38** and **39**),[102–106] carbonates (**40**),[82,97,103,107] and alkoxy acrylates,[107] as well as from phosphates (**41**), sulfites, and sulfates[108] (Scheme 15). Similarly, aldehydes or ketones are generated from enol esters (such as **42**)[102–104] and oximes from oxime carbonates.[109] Carbonate **40** allows the consecutive release of phenethylol by enzymatic or hydrolytic cleavage of the carbonate ester, followed by intramolecular cyclization to give a γ-decalactone and citronellol as additional fragrance molecules in a multistep sequence.[82] 4-Hydroxy carboxylates (such as **43**) and 4- or 5-hydroxyamides simultaneously liberate a lactone together with an alcohol or an amine, respectively (Scheme 15).[82,110] Organosilicon derivatives such as **42** may be used to increase the deposition of the precursors on the target surface.[104]

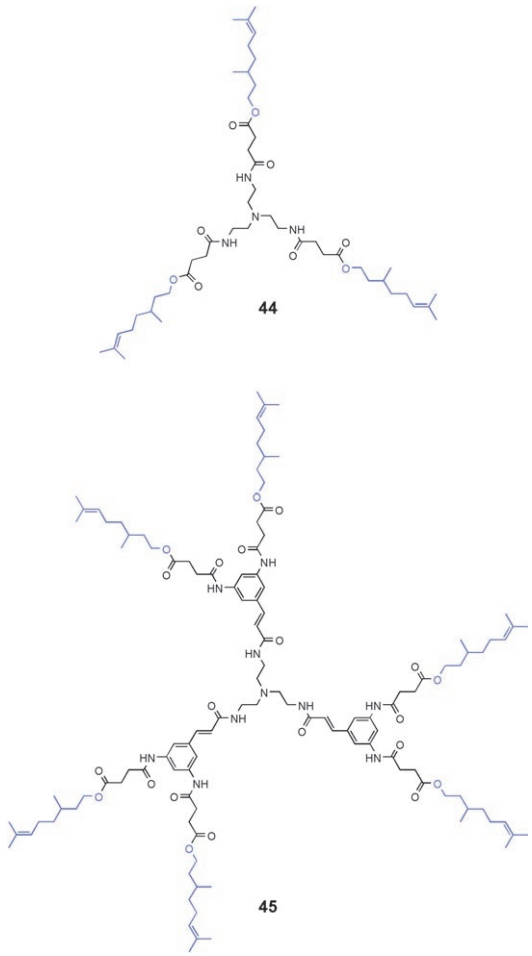


Scheme 15. Precursors for hydrolase (lipase) activated release of fragrances.

If the enzyme is separated from the fragrance precursor to be cleaved, the pro-fragrances are relatively stable during product storage. In laundry applications, for example, the fragrance precursor is added to the fabric softener rather than to the enzyme-containing detergent, and the two components are then deposited together onto the laundry in a typical washing cycle. Normal humidity was found to be sufficient for an efficient release of the fragrance. Textiles washed with a detergent powder containing lipase (lipolase 100T), followed by a rinsing cycle with a fabric softener containing **38** showed the desired long-lasting effect of fragrance release relative to the unmodified fragrance in a panel evaluation.[102] Most of the test persons detected a significantly more pronounced odor in the samples containing the fragrance precursors than in the reference samples. Based on this technology, digeranyl succinate (**38**)—or the corresponding product obtained from a mixture of geraniol and nerol—and later hexarose (**39**) were commercialized as pro-fragrances in fabric softener formulations.[102,105]

The ability of lipases to act on polymers has resulted in polymeric[111] and dendritic substrates[112] being proposed as carrier materials for the enzyme-triggered release of terpene alcohols. Hayes and co-workers synthesized a series of branched polyamides which were conjugated through ester linkages to primary or secondary fragrance alcohols.[112] Hydrolysis experiments carried out with a lipase (from *Candida cylindracea*) or a cutinase (from *Fusarium solani pisii*) in an aqueous buffer at pH 7.2 showed that the increase of bulkiness and rigidity arising from larger dendrimer sizes results in a decrease in cleavage of the alcohol. Under the conditions of their study, the cutinase was found to be more efficient than the lipase: In the presence of the lipase, citronellol was released from dendrimer **44** but not from **45** (Scheme 16), whereas the cutinase cleaved the ester bond in both compounds. The fact that secondary alcohols could not be released underlines the high selectivity of the enzymes for the hydrolysis of esters of primary alcohols.[112]

Proteases represent another group of hydrolases commonly used in detergents to remove proteinaceous stains.[100,101] N-acylated amino acids esters of different fragrance compounds were prepared by esterification of *N*-acylamino acids with fragrance alcohols or enolates.[113] Static headspace analysis showed that the amount of fragrance released from the fabric after a washing cycle with a protease-containing detergent and a fabric softener containing the precursor was significantly higher than in the absence of the enzyme.



Scheme 16. Dendritic substrates for enzymatic release of the fragrance.

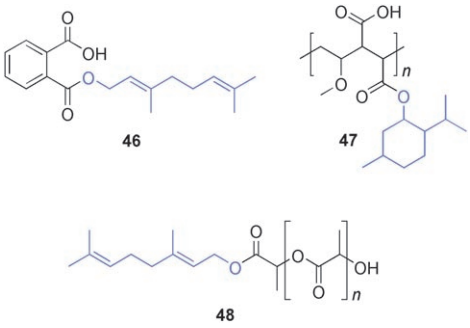
6. Hydrolysis and Change of the pH Value

Although the release of volatiles from various substrates in the presence of enzymes or microorganisms is quite efficient under neutral conditions, this technique can not be used in functional perfumery in every desired case. Enzyme activity may be insufficient under certain application conditions and, despite increasing success in the development of new enzymes by bioengineering, consumers are more and more suspicious of their presence in consumer articles. Side effects, such as allergic reactions or other skin irritations may be related to the activity of enzymes, and have resulted in the development of a series of enzyme-free bodycare or household products, which require alternative fragrance-delivery techniques.

Water is the medium used for most perfumery applications and hydrolysis, possibly induced by a change in the pH value, may thus be a suitable trigger to control the release of volatiles and to achieve an increased longevity of the fragrance perception. Typical examples are all kinds of washing processes, in particular laundry treatments, where the product is stored under alkaline (detergents and soaps) or acidic conditions (fabric softeners, body lotions, and shampoos) before being brought to a neutral pH value at the end of the washing cycle. In fact, most of the literature describing chemical-delivery systems for volatiles is based on hydrolytic bond cleavage of a broad variety of different precursors.

6.1. Carboxylates

Esters (to release alcohols)[105,114] or enol esters (to generate aldehydes or ketones)[115] are the most obvious precursors to be considered in this context. Suitable profragrances can generally be easily prepared from inexpensive starting materials. Monoesters of carboxylic diacids were obtained by reaction of a fragrance alcohol with maleates, succinates, or phthalates (**46**, Scheme 17).[114] This approach

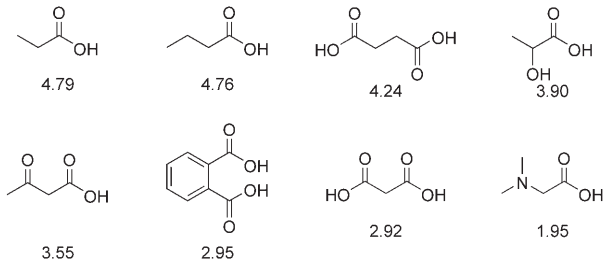


Scheme 17. Monomers and polymers for the release of volatile alcohols by hydrolysis of an ester bond.

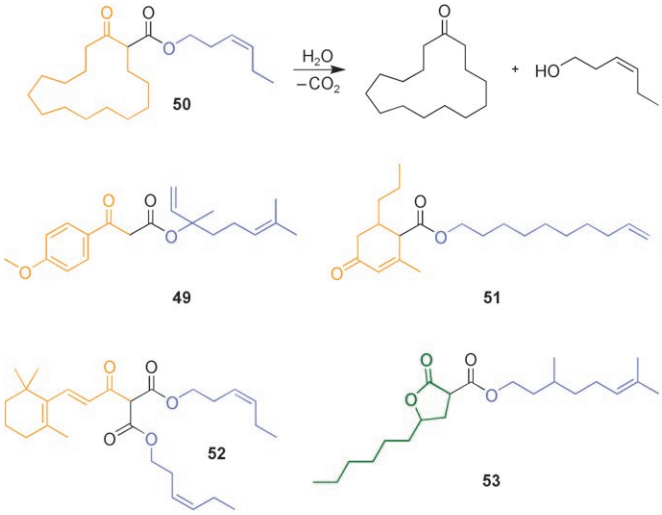
was also successfully used to prepare amphiphilic polymers and co-polymers (**47**) by treating the corresponding alcohol with materials containing maleic anhydride.[116] Biodegradable polyesters, such as **48**, were prepared by polycondensation of the corresponding carboxylic acids, followed by esterification with the fragrance alcohol.[117] Most of these substrates may be used for both enzymatic- or water-based hydrolysis. Whereas skin enzymes and bacteria work efficiently under neutral conditions,[108] aqueous ester hydrolysis requires acid or base catalysis and thus occurs only to a limited extent at a neutral pH value.

Ester hydrolysis is facilitated by decreasing pK_a values of the corresponding carboxylic acids[118] and, depending on the targeted application, the speed of hydrolysis can thus be influenced by the molecular structure of the carboxylic acid (Scheme 18). β-Keto esters (**49** and **50**)[119,120] (the corresponding 3-oxobutyric acid has a pK_a value of 3.55), unsaturated δ-keto esters (**51**),[121] and some malonate derivatives (**52** and **53**;[120,121] $pK_a = 2.92$ for the corresponding malonic acid) have been explored by Sivik and co-workers, as well as by Anderson and Fráter as substrates for the slow release of alcohols (Scheme 19). They can be hydrolyzed with subsequent decarboxylation under acidic or alkaline conditions and by the action of enzymes or heat,[122] and allow the simultaneous or successive release of different organoleptically or antimicrobially active compounds.

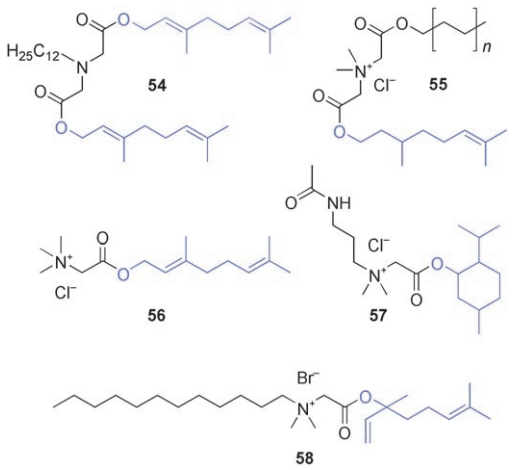
Depending on the precursor structure, an alcohol is obtained together with a fragrance ketone or lactone, and even tertiary alcohols, such as linalool (from **49**) were



Scheme 18. pK_a values of mono and dicarboxylic acids.[118]



Scheme 19. Hydrolysis of β-keto esters to form equimolar amounts of volatile alcohols and ketones or lactones.



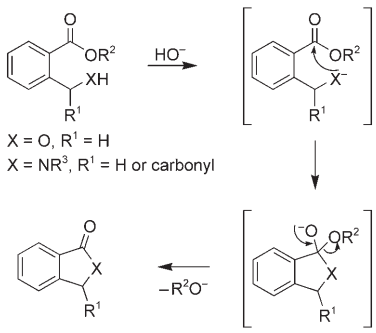
Scheme 20. Hydrolytic release of primary, secondary, and tertiary alcohols from α-amino esters and betaine esters.

successfully released. Headspace analysis on wet and dry fabric showed that in both cases the amount of fragrance detected in the samples containing one or several of the precursors **50**–**53** was higher than with the corresponding reference samples.[120,121]

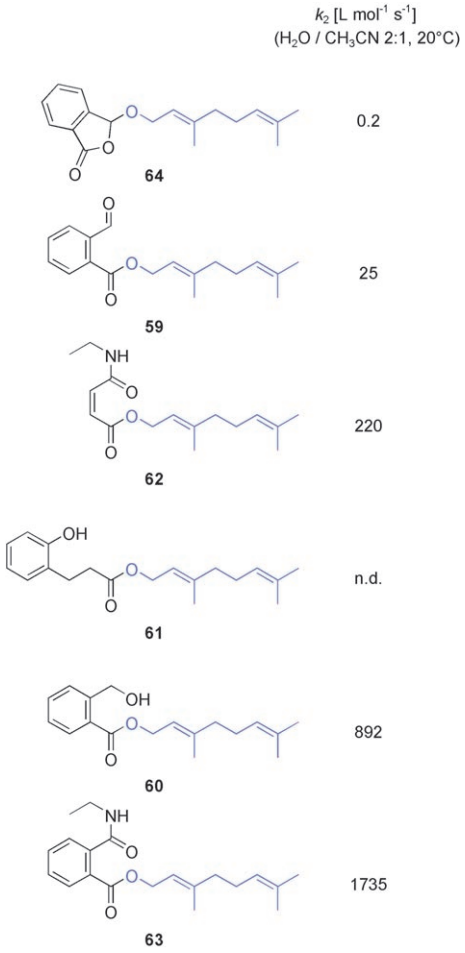
Glycine esters (such as *N*,*N*-dialkyl- or *N*,*N*,*N*-trialkylglycines (betaine esters)), with pK_a values of the corresponding carboxylic acids of about 2.00, are even more readily hydrolyzed. Tertiary or quaternary α-amino ester derivatives such as **54**–**58** (Scheme 20) have been reported as being stable in alkaline media and release the alcohol as a consequence of a drop in the pH value after dilution. Whereas α-amino esters have to be protonated prior to hydrolysis,[123] the structurally related betaine esters **55**–**58** (Scheme 20) can be directly hydrolyzed upon contact with water or by normal humidity.[124,125] Furthermore, the quaternary ammonium moiety increases the surface deposition of the compound as a result of its close structural relationship to cationic fabric softeners,[126] thus enhancing the efficiency of the precursors in cleaning and laundry products.[124] Betaine esters have also been explored for the development of cleavable surfactants.[127,128]

The hydrolysis of the betaine esters is strongly pH-dependent[124,125,129] and, as a consequence of their micelle-forming properties, further increased by micellar catalysis.[128] Betaine ester **56**, for example, is completely hydrolyzed within about 20 minutes under alkaline conditions (pH > 8) and only by about 20% after one hour under acidic conditions (pH < 6).[124] Betaine esters can be stabilized in alkaline media with anionic surfactants, as shown by comparing the kinetic rate constants and half-life times determined at 40 °C and at pH 8.5 and 10.5. Comparitive olfactive panel evaluations of the betaine esters with the corresponding unmodified reference fragrance alcohol in fabric softeners showed a significantly better performance for the former substrate. This was especially the case after several days to one week on dry fabric. Polymers stabilize the ester groups and result in reduced product release during storage. Low-molecular-weight polymers such as poly(ethyleneimines) (PEI), cross-linked PEIs, as well as partially ethoxylated or quaternized PEIs were found to be particularly effective.[130]

In analogy to enzymatic systems, where the efficiency of a reaction is often based on the presence of a specific functional group in proximity to the substrate to be formed or cleaved, intramolecular reaction pathways for the cleavage of carboxylic esters by an intermediate nucleophilic species have been developed. This principle is known as neighboring-group participation[131] or intramolecular catalysis[132] and has already been applied to the design of pro-drugs.[133] *Ortho*-substituted benzoates, and also some maleates and succinates, are able to release fragrance alcohols by intramolecular neighboring-group-assisted cyclization under alkaline hydrolysis conditions (Scheme 21).[134–137] For the cyclization to be efficient, the distance between the nucleophile and the ester bond to be cleaved should ideally be less than 2.8 Å and the total energy to adopt this conformation should not be more than 3 kcal mol^{-1} higher than the energy minimum of the molecule.[134] Compounds fulfilling these requirements include 2-acyl benzoates (**59**),[134,136,137] 2-(hydroxymethyl) benzoates (**60**),[134,137] dihydro coumarates (**61**),[134] as well as 3-carbamoyl propenoates (**62**) and benzoates (**63**)[135,137] (Scheme 22). 2-Carbamoyl benzoates were found to be particularly suitable for the release of tertiary alcohols, which are in general poor leaving groups for this type of reaction. The generation of the nucleophile is pH-dependent



Scheme 21. General principle of the controlled release of alcohols by neighboring-group participation.

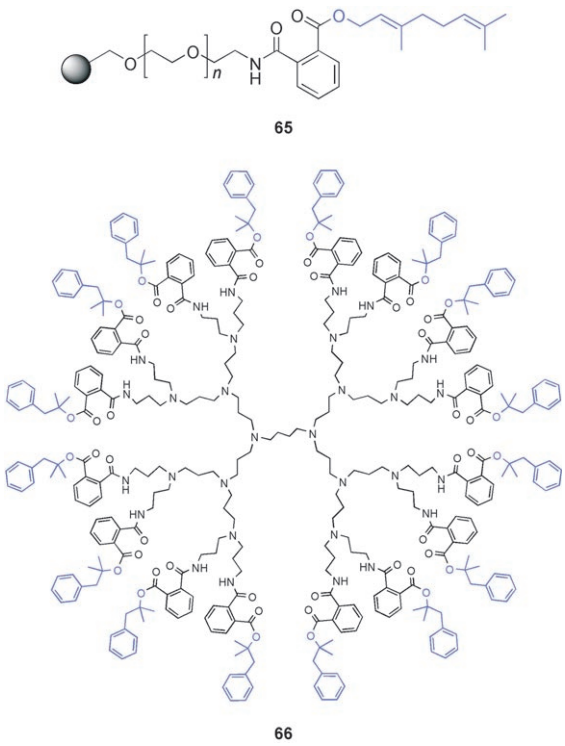


Scheme 22. Comparison of rate constants for the release of geraniol from different substrates by neighboring-group participation (k_2 in water/acetonitrile 2:1; n.d. = not determined).[137]

to its corresponding phthalide **64**, which can also release a fragrance alcohol, as a result of the formation of a similar reaction intermediate.[136] However, the structurally related phthalates (**46**) discussed previously do not release fragrance alcohols by neighboring-group participation.[139]

The rate constants for a series of precursors were measured by UV/Vis spectroscopy and HPLC in water/acetonitrile (2:1) at different pH values.[136,137] The rate constants were found to depend on the structure of the leaving alcohol (esters of primary alcohols hydrolyze faster than those of tertiary alcohols) as well as on the nature of the attacking nucleophile. The rate of release for the same alcohol can be varied over several orders of magnitudes by varying the precursor skeleton, as shown in Scheme 22 for the release of geraniol,[137] which allows adaptation of the delivery system to the required release rate for the targeted application.

The ease of preparation and the efficient release of tertiary alcohols[137] has resulted in 2-carbamoyl benzoates being chosen as substrates for the functionalization of amino groups in polymers (**65**) and dendrimers (**66**) (Scheme 23).[140,141] The excellent separation of the parent



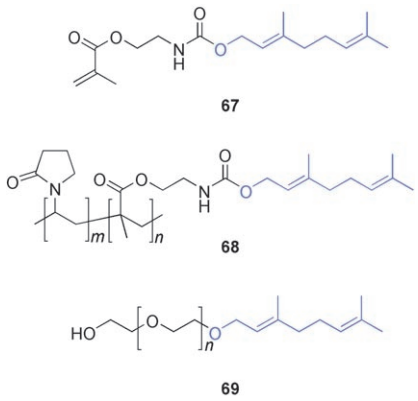
Scheme 23. A polymeric and dendritic 2-carbamoyl benzoates as precursors for the controlled release of alcohols by neighboring-group participation.

and generally occurs at neutral or slightly alkaline conditions, which render the compounds relatively stable under acidic conditions. Whereas 2-(hydroxymethyl) and 2-carbamoyl benzoates as well as dihydro coumarates can be directly deprotonated to generate the nucleophile, 2-acyl benzoates require hydration of the carbonyl group to allow intramolecular cyclization.[138] 2-Acyl benzoate **59** is closely related

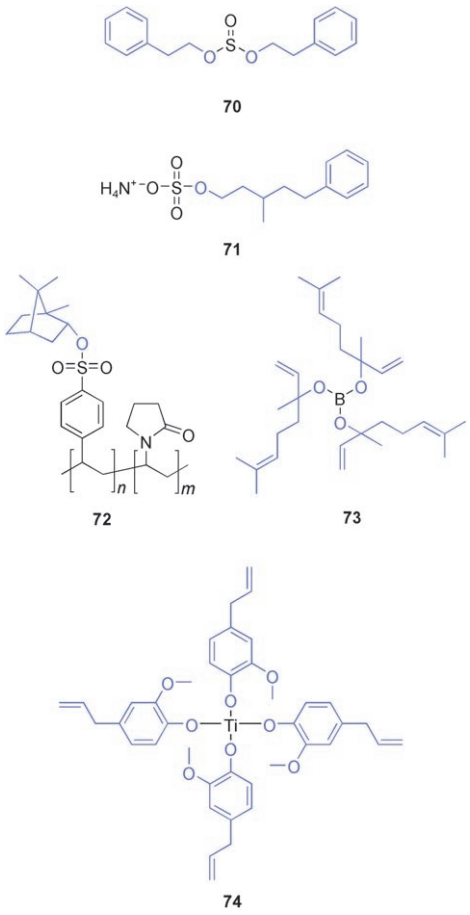
dendrimer **66** from its monocyclized intermediate by HPLC allowed the determination of the rate constants for the first two cyclization steps.[141] It was shown that the release kinetics are not influenced by steric effects and are thus independent of the dendrimer size. The fact that no enzymes or other bulky reagents are needed to release the active substances from the dendrimer surface allows the preparation of large molecules

with a high surface loading capacity with respect to the total mass of the delivery system. The release of the fragrance molecules from polymeric structures[140] is much slower than from for the corresponding low-molecular-weight compounds, thus indicating an increased stabilization of the release system within the polymer structure.

The reaction of alcohols with isocyanates yields carbamates (urethanes), which are reasonably stable in aqueous solution. A series of monomeric and polymeric carbamates[142,143] were prepared and their hydrolysis studied in strongly acidic media. Comparison of the amount of alcohol released from methacrylate **67** and its corresponding co-polymer **68** (Scheme 24) in concentrated HCl/dioxane gave



Scheme 24. Precursors for the release of alcohols from carbamates and alkoxy ethers by hydrolysis in acidic media.



Scheme 25. Inorganic esters of volatile alcohols and phenols.

comparable results. However, the solubility of the polymer in the reaction medium was found to be an important parameter, as sparingly soluble materials are only hydrolyzed to a small extent or not at all.[143] Even more stable are alkoxy ethers of fragrance alcohols, such as **69**, which, besides the desired slow release effect of the alcohol, give rise to increased tactile properties in hair-care applications.[144]

6.2. Inorganic Esters

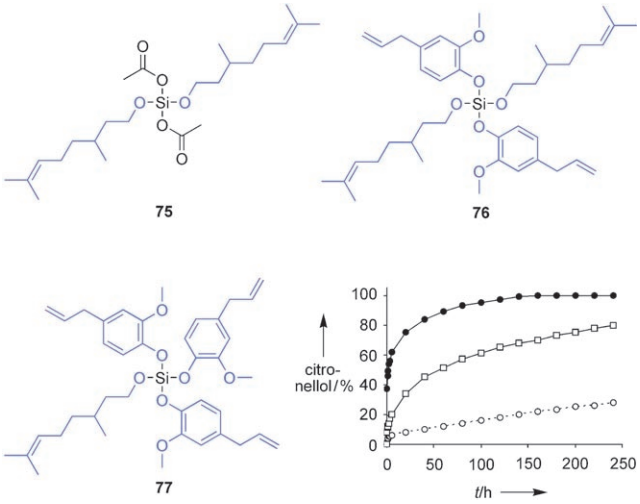
A series of inorganic esters of fragrance alcohols, in particular phosphates (**41**), sulfites (**70**), sulfates (**71**),[108] and sulfonates (**72**),[145–147] as well as borates (**73**),[86,148] aluminates,[149] zirconates, and titanates (**74**)[150] have been reported (Scheme 25). Sulfonates are readily accessible by reaction of the volatile alcohols with sulfonyl chlorides in the presence of a base. The use of *p*-vinylsulfonyl chloride allows the preparation of polymers and co-polymers.[145] Kamogawa et al. compared the release of alcohols from co-polymers containing a high amount of poly(vinyl pyrrolidone) with that from the corresponding monomers. As a result of steric hindrance, random co-polymer **72** released only about half the amount of borneol as the corresponding monomer after one week in a solution of dioxane/water (5:1).[145] Whereas esters of primary and secondary alcohols could easily be prepared, the esterification of tertiary alcohols was unsuccessful.

Although borates, aluminates, and titanates allow the slow release of primary, secondary, as well as tertiary alcohols, they are hydrolyzed at normal humidity and they are thus preferentially used in solid product formulations such as soaps, detergent powders, and deodorants.[86,148–150] The same is true for silanes and siloxanes, which represent the most important class of inorganic substrates for controlling the evaporation of volatiles.

6.3. Silanes and Siloxanes

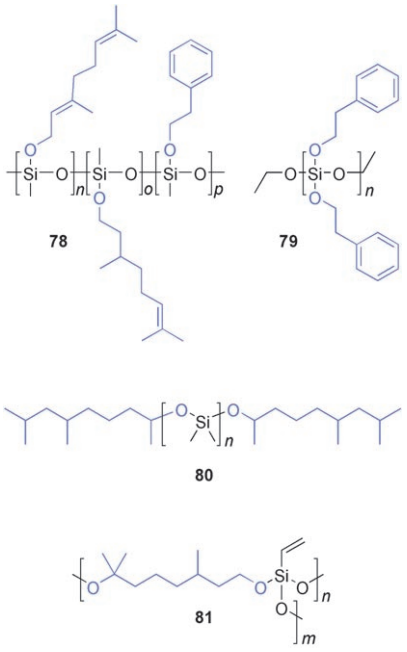
Silane pro-perfumes are prepared by replacing one or more halogen or hydrogen atom or alkoxy, acyloxy, or amino group of silane or silane derivatives by reaction with one or several volatile alcohols.[151–153] In general, product mixtures of mono- to tetrasubstituted species are obtained, and partial hydrolysis as well as condensation to form siloxanes is usually observed. As mentioned in the previous section on borates, aluminates, and titanates, the precursors gradually hydrolyze at normal humidity and the rate of hydrolysis is influenced by the amount of humidity as well as by the number and size of

the organic groups attached to the silicon atom. Scheme 26 shows a comparison of data obtained for the hydrolysis of precursors **75**–**77** in aqueous solution at 20 °C over a period of 240 h.[152] It was found that the rate constants increase as the number of acyl groups increase and the size of these groups decrease. In the absence of acyl groups, the rate of hydrolysis can be controlled by replacing the alkoxy groups with phenol derivatives (vanillin or eugenol), which results in an increased rate of release of the aliphatic alcohol (citronellol) from the molecule.



Scheme 26. Structure-dependent hydrolysis of siloxanes **75** (●), **76** (○), and **77** (□) in aqueous solution at 20 °C.[152]

Polysiloxanes which release either one specific fragrance alcohol or mixtures of different alcohols, such as **78** (Scheme 27), are obtained by treating the respective fragrance alcohols or mixtures thereof with poly(methylhydrosiloxane) (PMHS).[153,154] The fragrance alcohol is regenerated when the polymer is brought into contact with an aqueous solution of NaOH or KOH. This procedure was originally developed for the industrial-scale reduction of carbonyl compounds,[155] and the utility of the intermediate polysiloxanes as controlled-release systems was discovered in the context of these studies. Transesterification of oligosilicates with single fragrance alcohols or alcohol mixtures allows the preparation of precursors such as **79**, wherein the substituents along the Si-O-Si chain are more easily exchanged than those at the chain ends.[156] Reaction of alkyl alkoxysilanes with cyclic siloxanes results in polymers of type **80**, in which the fragrance alcohols are located at the two ends of the siloxane chain.[157] The reaction of vinyl trichlorosilane with a diol such as hydroxycitronellol results in a branched polymeric structure (**81**) in which the fragrance diol is part of the polymer backbone (Scheme 27). The hydrolysis of **81** in aqueous solution to release the diol was found to be pH-dependent, and accelerated as the pH value decreased.[158]



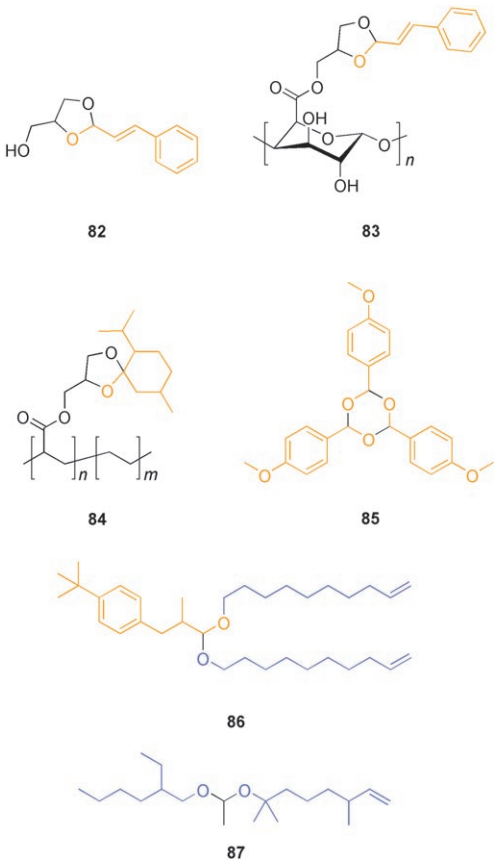
Scheme 27. Hydrolytically cleavable polysiloxanes.

6.4. Acetals, Ketals, and Related Structures

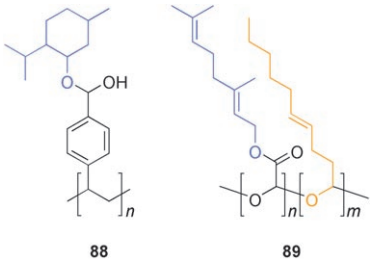
Whereas alcohols are in general reasonably stable during product storage and application, aldehydes suffer from partial degradation by oxidation, polymerization, and reactions resulting from the electrophilic carbonyl group. Chemical-delivery systems are particularly interesting in this context as they allow the labile aldehyde function to be masked by derivatization and regenerated later during product application. As a consequence of their structural similarity, volatile ketones can often be released from the same type of precursors.

Acetaldehyde and propionaldehyde are highly volatile and contribute significantly to the flavor impact of many natural products. They can be protected as acetals against degradation. Precursors suitable for food applications, such as in instant beverages, chewing gums, and other foodstuffs, were obtained by condensation of the aldehydes with food-grade ingredients such as ethanol or glycols.[159–162] Acetals and ketals, in particular those formed by reaction of carbonyl compounds with glycerol (**82**–**84**, Scheme 28),[162–164] are also interesting for a variety of perfumery applications. The remaining free hydroxy group of the 1,3-dioxolanes serves as an anchor to link the pro-fragrances to various polymeric supports such as in **83** and **84**.[163] When aldehydes self-condense to form cyclic trimers (**85**)[165] or when fragrance alcohols are used for the preparation of acetals (**86** and **87**),[165–168] fragrance mixtures can be released. Upon decomposition, 100 % of the precursor structure results in olfactively active compounds.

Kamogawa et al. prepared polymeric acetals by treating fragrance alcohols with vinylbenzaldehyde followed by radical polymerization of the acetal monomers.[169] Whereas primary alcohols such as citronellol and geraniol formed acetals in good yields, secondary alcohols such as borneol and menthol mainly gave hemiacetals (**88**, Scheme 29). Mixed polymers (**89**) that release volatile aldehydes and alcohols can



Scheme 28. Cyclic and acyclic acetals for the acid-catalyzed release of aldehydes and/or alcohols.

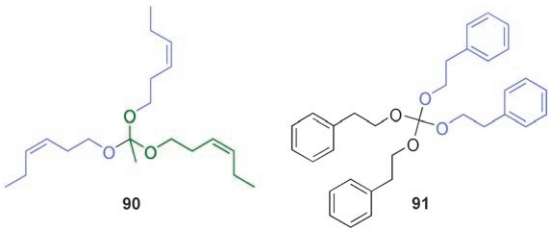


Scheme 29. Polymeric acetals and hemiacetals.

be obtained by co-polymerization of methyl glyoxylate and a fragrance aldehyde, followed by transesterification of the methyl ester with a fragrance alcohol.[170]

Hydrolysis of the acetals occurs mainly by general acid catalysis and the reaction rate is increased by the presence of polar substituents at the carbonyl group, and is strongly influenced by cationic (inhibition) or anionic (catalysis) surfactants.[171] Cyclic acetals (1,3-dioxolanes) were found to be more stable than the corresponding acyclic acetals.[160] As acetals are generally quite stable in the targeted applications of functional perfumery, less-stable variations of these compounds have been systematically investigated.

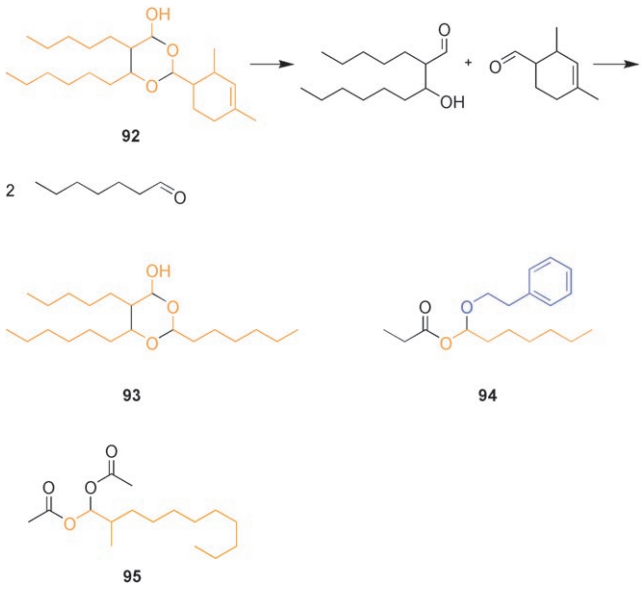
Orthoesters (**90**)[161,168,172,173] and orthocarbonates (**91**)[168,172] (Scheme 30) are structurally related to acetals and are prepared by the acid-catalyzed reaction of a fragrance



Scheme 30. Orthoesters and orthocarbonates for the release of alcohols in acidic media.

alcohol with an orthoester or an orthocarbonate. Whereas orthoacetate **90** hydrolyzes to form (*Z*)-3-hexenol together with its corresponding acetate, orthocarbonate **91** releases two equivalents of phenethylol together with di(phenylethyl)carbonate. This latter compound can further hydrolyze to yield two more equivalents of phenethylol.[168,172] These systems are very atom-economic, as all parts of the precursors are transformed into olfactively active compounds. The pH-dependent hydrolysis of orthoesters showed that under alkaline conditions (pH 9.5) the compounds are relatively stable and no fragrance was released, whereas under slightly acidic conditions (pH 6.5) the orthoesters completely hydrolyze within several hours.[161]

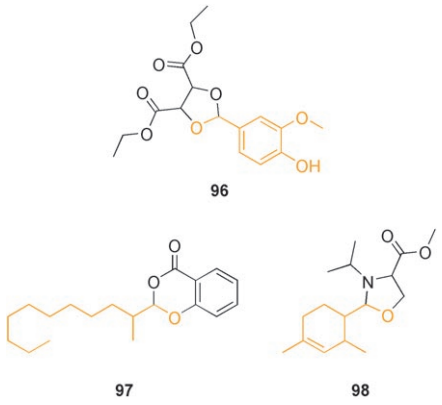
Aldoxanes (such as 1,3-dioxan-4-ol derivatives **92** and **93**) are formed by reaction of an aldehyde with an aldol.[174] The release of aldehydes is a two-step process in which a change in the pH value or heat is used as the trigger. In the first step an aldehyde and an aldol are formed, the latter of which may be a stable molecule or decompose either into an α,β-unsaturated aldehyde by elimination of water or into two further aldehydes by a retroaldol reaction (Scheme 31). The rate of aldehyde release can be influenced by the choice of the substituents on the aldoxane ring system. Womack et al. showed that besides hydrolysis, aldoxanes efficiently release



Scheme 31. Aldoxanes (**92** and **93**), alkoxy esters (**94**), and acylals (**95**) as aldehyde precursors.

aldehydes by thermolysis at 60–80 °C[174] and are therefore particularly useful for the release of aldehydes during tumble drying. Similarly, Eh et al. prepared alkoxy esters (**94**)[175] and acylals (**95**),[176] which, upon hydrolysis or the action of enzymes, simultaneously release different types of biologically active substances. Besides aldehydes, alkoxy esters release a carboxylic acid and an alcohol, and acylals release two equivalents of carboxylic acid (Scheme 31).

Further substitution of the acetal or ketal structures allows the stability of the precursors to be increased in neutral or slightly acidic media. Dicarboxydioxolanes of aldehydes, such as **96** (Scheme 32),[45] obtained by transacetalization of

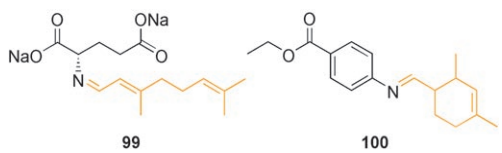


Scheme 32. Dioxolanes (**96**), dioxolanones (**97**), and oxazolidines (**98**).

dimethyl acetals with tartrates were found to be sufficiently stable in consumer products. Varying the bulkiness of the carboxylate ester groups[45] or increasing the temperature[44,45] allowed the fine-tuning of the aldehyde release. Other aldehyde-releasing compounds based on modified acetal structures comprise dioxolanones (**97**)[177] and oxazolidines (**98**).[178]

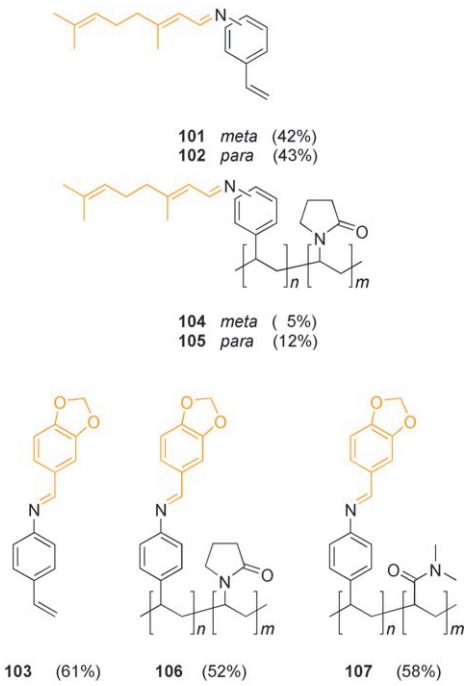
6.5. Imines

The hydrolysis of carbonyl-amine condensation products (imines, Schiff bases) was one of the first reactions that has been described for the release of flavor or fragrance aldehydes and/or ketones by hydrolysis in an aqueous environment.[179] Condensation products with urea, anthranilates, and glutamates (**99**) were prepared for food applications,[179] and Schiff bases of aminopropyl polysiloxanes,[180] amino acids, aromatic amines (**100**),[181,182] and polyamines[182–184] were synthesized for detergents and fabric softeners (Scheme 33).



Scheme 33. Schiff bases as labile aldehyde precursors.

In 1982 Kamogawa et al. prepared Schiff bases by reaction of perfumery aldehydes with *m*- or *p*-aminostyrenes.[185] With the exception of citronellal, where aldol condensation was observed as a side reaction, the corresponding imines (such as **101**–**103**, Scheme 34) were obtained in ethanol without

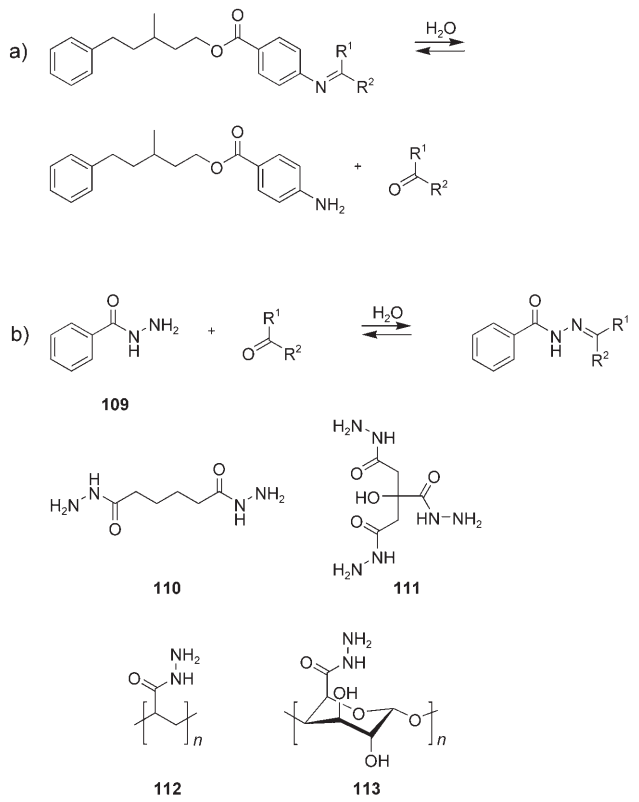


Scheme 34. Comparison of the release of aldehydes from monomeric and polymeric Schiff bases. The values in brackets indicate the amount of aldehyde isolated after hydrolysis in aqueous acetic acid for 48 h.[185]

heating. The *p*-Schiff bases were generally obtained in higher yields and had higher melting points than the *m* isomers. The monomers were co-polymerized by radical polymerization in the presence of *N*-vinyl-2-pyrrolidone or *N*,*N*-dimethylacrylamide to give water-soluble materials **104**–**107**.[185] Hydrolysis in aqueous acetic acid over 48 h showed that the *m*- or *p*-Schiff base monomers **101** and **102** as well as random co-polymers **104** and **105** give rise to a similar degree of hydrolysis when compared pairwise. However, the hydrolysis of citral (as the leaving aldehyde) from the polymers was found to be considerably slower than from the corresponding monomer (Scheme 34). In the case of heliotropin as the aldehyde to be released, similar amounts of volatiles were liberated from both the monomer **103** as well as from random co-polymers **106** and **107**.[185] As a consequence of their inherent instability in the presence of water, Schiff bases have either to be stored under dry conditions and only brought into contact with water during their use[179] or preferentially formulated at alkaline pH values.[180,181]

Another possibility to circumvent product stability problems consists of the in situ generation of the pro-fragrances as the so-called reaction products. Birkbeck et al. used amino benzoates as reversible trapping agents to control the release of carbonyl compounds from an equilibrium which is

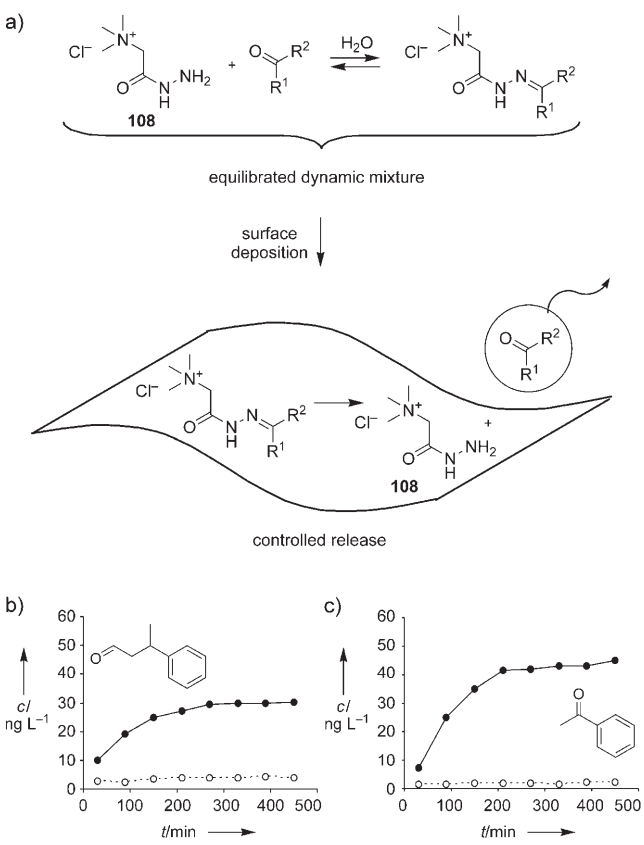
automatically set-up in a water-based environment (Scheme 35a).[181] Hydrazones, which are more stable than classical Schiff bases, are formed in a similar way by reaction



Scheme 35. Reversible formation and hydrolysis of imines from aryl amines (a) and hydrazides (b).

of hydrazine derivatives with a fragrance aldehyde or ketone in aqueous solution (Scheme 35b).[186,187] The reaction is reversible and reaches an equilibrium consisting of a mixture of the hydrazine derivative and the unmodified carbonyl compound together with the hydrazone formed by condensation of the two compounds.[188] Kinetic measurements carried out by UV/Vis spectroscopy in acidic buffer solutions showed that (at equimolar product concentrations) both the formation and hydrolysis of the hydrazones reached the same equilibrium state.[187] Determination of the kinetic rate constants showed that the formation of the equilibrium mainly depends on the pH value of the aqueous medium rather than on structural aspects of the hydrazine or the aldehyde or ketone.[187]

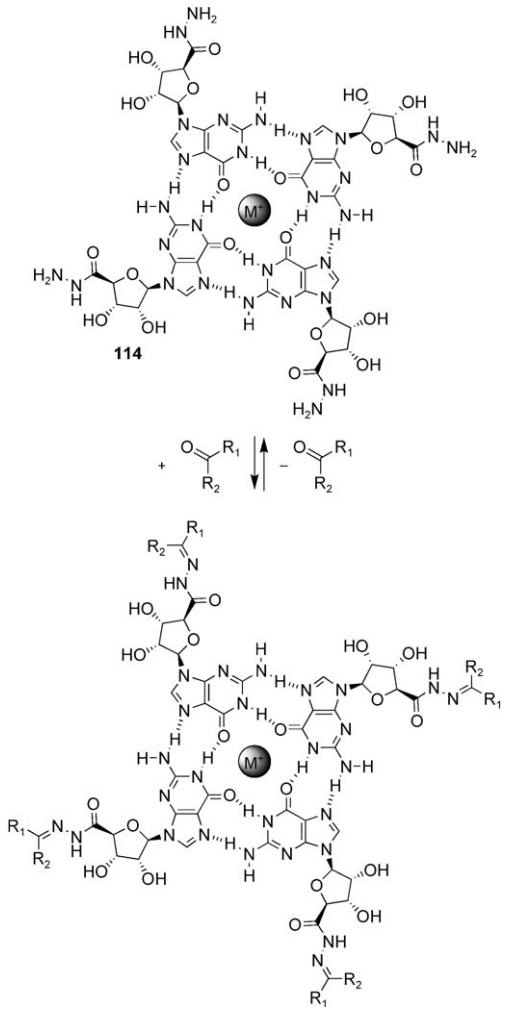
Reversible chemical reactions[189] have recently been used for the development of dynamic combinatorial libraries for drug discovery.[190] Acylhydrazones were found to be of particular interest in this context, as they incorporate both a peptide bond and a reversibly formed imine unit.[191] In contrast to pharmaceutical applications where the hydrazone is the targeted active species, the use of dynamic mixtures for the controlled release of volatile carbonyl compounds requires the full reversibility of the reaction to recover the active molecule from the transient hydrazone. Some hydrazides are commercially available, others can be easily prepared.[192] A broad variety of different alkyl and aryl hydrazides (such as **108**–**111**), including polymeric structures (**112** and **113**), have been investigated to control the release of fragrances (Schemes 35 and 36).[186] The addition of a hydrazide to a mixture of several aldehydes and/or ketones in the presence of water, for example, in a fabric softener formulation, results in the generation of a dynamic mixture.[186,187] A multitude of pro-fragrances are formed spontaneously, thus allowing the controlled release of a series of different carbonyl compounds simultaneously. Once the dynamic mixture is deposited on a surface, the fragrances evaporate and shift the equilibrium towards the free hydrazine derivative (Scheme 36). The performance of dynamic mixtures was evaluated after equilibrating a mixture of several volatile aldehydes and ketones for a few days in the presence and absence of a hydrazide derivative in a fabric-softening formulation. Dynamic headspace analysis on the dry fabric after the washing cycle showed that the presence of the hydrazide had a significant effect on the evaporation of the fragrance aldehydes and ketones in the mixture. The amount of aldehyde or ketone detected in the headspace of a sample containing equimolar quantities of the fragrances was up to 20 times higher in the presence of hydrazide **108** than



Scheme 36. Principle for the controlled release of fragrances from dynamic mixtures. a) The original equilibrium is shifted by slow evaporation of the fragrance from the surface. b) c) The graphs show the difference in dynamic headspace concentrations of trifernal (b) and acetophenone (c) measured by evaporation of the fragrance from dry cotton in the presence (●) or absence (○) of hydrazide **108**.[186,187]

the reference without **108** (Scheme 36).[186,187] It was found that the increase in the headspace concentration in the presence of the hydrazide is particularly efficient for the most volatile carbonyl compounds (although there is no direct linear correlation between the headspace concentration and the volatility of the carbonyl compound).[187]

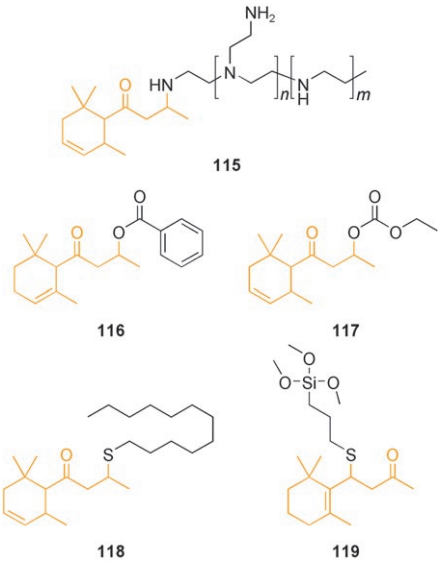
Recently Sreenivasachary and Lehn reported the preparation of guanosine-5′-hydrazide (**114**)[193] which forms, like guanosine itself, supramolecular hydrogels through selective self-assembly to a guanine quartet (G-quartet) structure in the presence of alkali-metal cations (Scheme 37).[194] As a consequence of the hydrazide group, the G-quartet structure of **114** can be functionalized by reversible formation of an acylhydrazone with carbonyl compounds. It was found that if a mixture of aldehydes is added during the formation of the gel, the dynamic system selectively chooses the compound which gives rise to the most stable hydrogel.[193] Hydrogels formed from **114** were found to be interesting carriers for biologically active substances, such as aldehydes or ketones, as they can be trapped not only by noncovalent interactions, but also through the formation of a covalent bond within the hydrogel structure.[195] The comparison of hydrogels formed from guanosine, where only noncovalent interactions with the guest molecules are possible, with those based on hydrazide **114** showed that the latter were significantly more stable than the former. An increased longevity in the release of fragrance from hydrogels of **114** relative to those formed from guanosine was shown by dynamic headspace analysis.[195] Hydrogels formed from **114** thus allow not only the controlled release of volatile aldehydes or ketones by reversible formation of a hydrazone, but also the selective aggregation of the pro-fragrance into a well-ordered three-dimensional supramolecular structure.



Scheme 37. Reversible formation of acylhydrazones from carbonyl compounds by reaction with guanosine-5′-hydrazide (**114**) within a self-assembled supramolecular hydrogel structure. M^+ = alkali-metal ion.

6.6. 1,4-Addition Products

α,β-Unsaturated ketones (such as damascones and ionones),[20] as well as unsaturated esters and acids and nitriles, react with amine derivatives to form β-amino ketones by a 1,4-addition rather than imines by reaction with the carbonyl function.[182,196] The 1,4-addition products are more stable than the corresponding Schiff bases. Busch and co-workers prepared a reaction product of α- or δ-damascone with PEI (**115**, Scheme 38),[182] which was commercialized as a delivery system for the corresponding rose ketone in detergent powders. Pro-fragrances obtained by the reaction of damascones or ionones with O and S nucleophiles were developed by Fehr et al.[197,198] Alcohols as well as alkyl thiols add to the double bond of damascones and ionones under basic reaction conditions and allow the preparation of various addition products. With the addition of O nucleophiles being less efficient than that of S nucleophiles, precursors **116** and **117** (Scheme 38) were prepared in a two-step sequence via their corresponding aldol, whereas pro-fragrances **118** and **119**



Scheme 38. Different 1,4-addition products of rose ketones and ionones using nitrogen (**115**), oxygen (**116** and **117**), and sulfur (**118** and **119**) nucleophiles.

could readily be obtained in one reaction step.[197,198] Thioether **118** was found to be very efficient for the controlled release of δ-damascone in fabric-softener applications, as shown by dynamic headspace analysis on dry fabric after three days. Figure 4 shows that significantly higher headspace

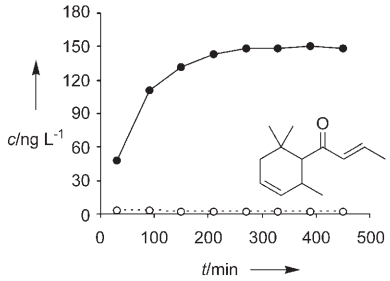


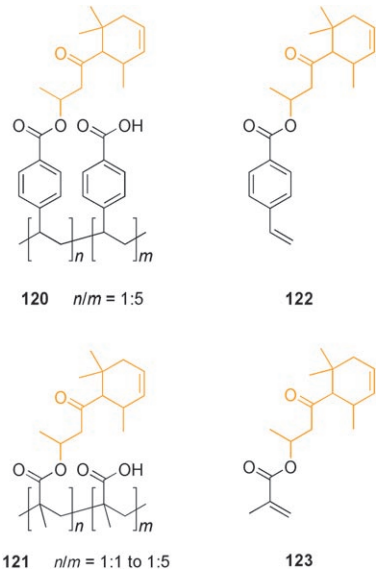
Figure 4. Dynamic headspace analysis on dry cotton for the controlled release of δ-damascone from pro-fragrance **118** (●) in comparison to an equimolar amount of free δ-damascone as the reference (○).[199]

concentrations of δ-damascone were measured for the release from **118** as compared to an equimolar amount of unmodified δ-damascone.[199]

The 1,4-addition of O and S nucleophiles to α,β-unsaturated ketones was found to be very flexible, which allows the preparation of a broad variety of delivery systems with different material properties. Precursor **119**, for example, was attached to modified silica powder to form inorganic silica nanoparticles. These systems can be used to form dispersions in a liquid environment, which are often more stable than emulsion-based systems in a consumer product formulation.[200]

Amphiphilic polystyrene- and polymethacrylate-based β-acyloxy ketones **120** and **121** were prepared by radical co-polymerization of the corresponding monomers **122** and **123**, respectively (Scheme 39). Co-polymers of the amphiphilic polymethacrylates **121** were prepared with different stoichiometric ratios between the fragrance release unit and the carboxylic acid containing co-monomer to study the influence of structural changes on the retro-1,4 addition reaction.[201,202] The carboxylic acid functions of the co-monomer are hydrophilic and thus allow a better dispersion of the polymer in aqueous media in comparison to more hydrophobic polymer structures. They are furthermore expected to undergo a pH-dependent change in conformation—from strongly coiled at low pH values to unfolded at higher pH values—as a consequence of an increasing deprotonation of the carboxylic acid group with increasing pH value.[203]

A comparison of the release of damascone from monomers **122** and **123** and from random co-polymers **120** and **121** in an alkaline-buffered aqueous solution showed that the release of the fragrance from the polymeric system is considerably slower,[201] as was previously seen for the hydrolysis of polymeric carbamoyl benzoates[140] and imines.[185] Fluorescence probing and solvent extraction measurements over several days and at different pH values showed that the polymers were stable in acidic media, whereas an increasing amount of damascone was found to



Scheme 39. Amphiphilic β-acyloxy ketones based on polystyrene and polymethacrylate for the controlled release of δ-damascone by retro-1,4-addition.

be released over time in neutral or alkaline solution. The fluorescence measurements further showed that in the case of **121** the hydrophilicity of the polymer backbone increased with increasing release of the fragrance, whereas in the case of **120** an almost constant hydrophilicity was measured.[201] These results suggest that the nature of the polymer backbone, and thus the hydrophilicity or hydrophobicity of the local environment in proximity to the release unit, has a strong influence on the rate of release of the fragrance.

7. Discussion

Despite the limitation of the reaction conditions to (small) changes in the pH value or temperature and the presence of oxygen, daylight, enzymes, or water, a broad variety of different precursors have successfully been developed to control the release of volatile organic compounds by cleavage of a chemical bond. Mild reaction conditions of our everyday environment are sufficient to trigger the cleavage of covalent bonds and thus allows organic chemistry—typically associated with reaction flasks, solvents, and special reagents—to be brought into common consumer products. The large number of patent applications published on this topic underlines the strong interest in pro-fragrance technologies. Nevertheless, the fact that only a few of the products described above have been successfully commercialized or are currently on their way to the marketplace also shows that there are many constraints to be considered for the successful commercialization of these types of products.

In classical organic synthesis the reaction pathway is selected as a function of the structure of the compound to be prepared, whereas chemical-delivery systems have to be designed according to the trigger and thus the organic reaction that is available for the release. This means that it

is the environment of the targeted application that finally decides on the structure of the precursor to be developed. Delivery systems which can be used in a broad variety of different products have to be able to respond to various types of triggers and are therefore the exception rather than the norm. Alkaline washing powder and liquid detergents require completely different precursor structures than acidic fabric softeners, while body lotions have different specifications to soaps, shampoos, and cosmetic creams. Nevertheless, some very general aspects, which will now be discussed in further detail, are equally important for all kinds of pro-fragrance technologies.

7.1. Precursor Stability

One of the most important criteria for the successful development of pro-perfumes is to achieve a high product stability prior to use. An efficient decomposition of the precursor under mild environmental reaction conditions on the one hand and a high product stability during storage on the other hand are two opposite conditions which are generally not easy to achieve (Figure 5). In particular, if the

Figure 5. The pro-fragrance stability and release efficiency paradox.

precursor has to be kept in the presence of the trigger—as is the case for all oxygen-sensitive release systems and for hydrolytically labile pro-fragrances in liquid consumer products—only a compromise can be achieved between the precursor stability and an efficient release of the fragrance. All of the commercialized pro-fragrances mentioned above are not exposed to their trigger during product storage. Light-activated precursors such as **28**[76] can be stored in the dark by choosing opaque packaging materials, esters **38** and **39** are incorporated in fabric-softener formulations and combined in the application with a lipase-containing detergent as a two-component system,[102] and the hydrolytically unstable reaction product **115**[182] is used as an ingredient in solid detergent powders.

As a consequence of their macroscopic character and the possibility to tailor their physicochemical properties, polymer conjugates represent an important opportunity to stabilize labile covalent bonds and may thus help to find a good compromise between release efficiency and product stability. A comparison of polymeric pro-fragrances and their corresponding monomeric low-molecular-weight analogues showed that the fragrance release is generally slower in a polymeric environment, thus indicating a strong stabilizing effect of the polymer structure.[140,185,201] Besides the stabilizing effect, amphiphilic polymer conjugates are furthermore expected to facilitate the dispersion of hydrophobic actives in aqueous media, and help to selectively deliver the volatiles to various target surfaces.

A specific and interesting example that addresses the issue of precursor stability are dynamic mixtures, which form reversible equilibria in aqueous media.[186,187] As long as the individual ingredients involved in the formation of the dynamic mixture are stable by themselves and not involved in side reactions, the proportion of the pro-fragrance in the equilibrium is only defined by external parameters (such as concentration, temperature, pH value, humidity, the presence of surfactant, etc.) to which the mixture is exposed during product storage. This situation means that the same stable and reproducible equilibrium is spontaneously reached if the same parameters are applied, and even a shift of the equilibrium can always be corrected by resubmitting the product to the original conditions. The complete reversibility of the system thus ensures that precursor stability is not an issue for dynamic mixtures.

7.2. Biocompatibility

While the inherent instability of the precursors is a challenge during product storage, it certainly is a clear advantage for the required biocompatibility of the compound. The fact that the delivery systems are designed to decompose under mild environmental conditions facilitates their biodegradation, which is an absolute prerequisite for the registration of any new molecules that are brought to the marketplace. Nevertheless, all parts of the molecule have to be considered for their complete biodegradability. Whereas this is generally the case for the fragrance materials themselves (which have already undergone registration), the remaining part of the precursor may have to be tested separately for its biocompatibility. For perfumery applications, where a less severe procedure for the registration of new compounds is applied than for flavors, flavor ingredients, and pharmaceuticals, general toxicity, mutagenicity, and skin irritation are the major safety testing procedures used. Since general predictions of toxicity based on precursor structures are not possible, this hurdle has to be cleared by each compound individually and, therefore, generally represents the last step before the introduction of new ingredients.

7.3. Cost Efficiency

Economically successful delivery systems of volatiles in consumer products furthermore require performing and cost-efficient solutions. The relatively low market price of mass-consumed articles, such as household or bodycare products, means there is almost no financial margin to incorporate expensive delivery technologies. This situation generates an important pressure on the cost of the corresponding precursor and therefore has a strong impact not only on the choice of the release system, but also on the volatile compound itself.

Expensive raw materials can only be used if the pro-fragrance has a strong advantage over the free fragrance itself, for example, if a better deposition on the target substrate[15] or a more appropriate release rate during and after the application can be achieved. As many fragrances are soluble

to some degree in water and thus get easily rinsed away in a washing cycle, efficient deposition is a very important issue in the design of pro-fragrance delivery systems. In a first approach, hydrophobic materials are usually more readily deposited on different surfaces from a water-based medium than hydrophilic ones. The octanol/water partition coefficient ($\log P_{ow}$)[204] is the most generally used parameter to measure the hydrophilicity or hydrophobicity of fragrance raw materials. As a very general trend, fragrances with high log P_{ow} values are more readily deposited, and are therefore more substantive or long-lasting[12] than hydrophilic ones. This in turn suggests that besides influencing the volatility of fragrances, pro-fragrances may also efficiently reduce the hydrophilicity of polar fragrance raw materials, and thus generate a long-lasting effect as a result of an increased surface deposition, a fact which was confirmed by practical experience. The presence of surfactants in almost all household or bodycare consumer products is another aspect that influences the deposition of fragrance materials[205] and their precursors. The compounds can be incorporated into the micelles of the surfactant, which may then serve as a carrier to increase the deposition and also influence the release of the respective compounds. Cationic surfactants,[126] which are used in fabric softeners and hair conditioners, are known to have a high affinity to various surfaces. Cationic groups (as in **55**–**58** or **108**) have therefore been used preferentially as a part of the pro-fragrance substrate to increase the deposition of the precursors on different surfaces.

Pro-perfumes which release several different fragrance molecules from the same precursor molecule have the advantage of being more atom-economic than those generating only a single fragrance raw material together with a nonvolatile substrate that has no olfactory benefit. However, even if all the atoms of the pro-perfume can be transformed into biologically active volatiles, as is the case for several of the compounds described above, the individual molecules can only be delivered in a fixed stoichiometric ratio. This is not always what is required from the perfumer's point of view, and may therefore limit the flexibility of the perfume creation considerably. A reasonable weight ratio of the active volatile compound and pro-fragrance substrate has to be achieved for all types of precursors by keeping the percentage of the remaining nonvolatile substrate to a minimum. In most of the pro-fragrances discussed above, the weight of the active volatile compound with respect to the total mass of the precursor molecule is about 50 % and decreases in some polymeric materials to around 10 %, which is the lower limit for economic acceptance.

Furthermore, to be useful in consumer products, the precursors have to be readily prepared on a large industrial scale at low cost, typically close to that of the compound to be released, a factor which immediately prohibits complex multistep syntheses and the use of expensive raw materials. In the case of the commercial pro-fragrances mentioned above, the precursors can be prepared in a one-step synthesis from relatively inexpensive starting materials.

The development of dynamic mixtures as fragrance delivery systems offers several economic advantages with respect to "classical" pro-fragrances.[187] On the one hand, the precursors do not have to be synthesized individually, as they are formed spontaneously by simple addition of the corresponding substrate to a mixture of the fragrances in the form of a reversible equilibrium. On the other hand, a multitude of precursors is formed simultaneously as a mixture in a stoichiometric ratio that can be selected by the perfumer, which allows the evaporation of many different compounds to be prolonged at the same time. As a consequence of its simplicity and efficiency in controlling the release of volatiles, dynamic mixtures have great potential as future delivery systems in the flavor and fragrance industry.

8. Conclusion and Outlook

Mild environmental conditions, such as the action of temperature, oxygen, light, and enzymes, as well as hydrolysis reactions at different pH values, allow efficient control over the evaporation of volatile organic molecules by the cleavage of chemical bonds from suitably designed precursors. Up to now, the development of pro-fragrances has mainly been based on the investigation of possible precursor structures in regard to the various triggers available in our everyday environment. The limited possible reaction conditions together with the additional challenges imposed by the specific requirements of product stability, price, and biocompatibility of the precursors, may explain why only a few precursors have been commercialized so far. The large amount of patent literature available on this topic clearly underlines that a strong economic interest is one of the major driving forces for the development of novel and efficient delivery technologies.

Future investigations will presumably focus on understanding the interactions of the precursors with their direct environment. This includes a better comprehension of the chemical reactions taking place in organized media, such as in complex surfactant systems. Furthermore, enhanced and more selective surface deposition, control of the precursor stability within polymer conjugates or supramolecular assemblies, as well as a direct influence on the release rate by simple structural variations are highly desirable. This requires a truly interdisciplinary approach to apply our knowledge of organic chemistry to the understanding of complex biological and physical phenomena.

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