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Profragrance Chemistry as an Interdisciplinary Research Area and Key Technology for Fragrance Delivery

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Abstract: Profragrances or properfumes are important delivery systems for the controlled release of volatile compounds. They constitute an essential part of a series of commercial body care and household products to ensure the long-lastingness of perfume perception in practical application. Fragrances are released from their respective precursors by covalent bond cleavage under mild environmental conditions. Originating from organic chemistry, modern profragrance research has evolved to a truly interdisciplinary research area covering supramolecular science, physical chemistry, analytical chemistry and various aspects of materials science. The present report highlights some of the profragrance technologies developed at Firmenich during the past 20 years by focusing on hydrolytically cleavable conjugates and photolabile precursors.

Keywords: Delivery systems · Dynamic combinatorial chemistry · Neighbouring group participation · Photocages · Profragrances

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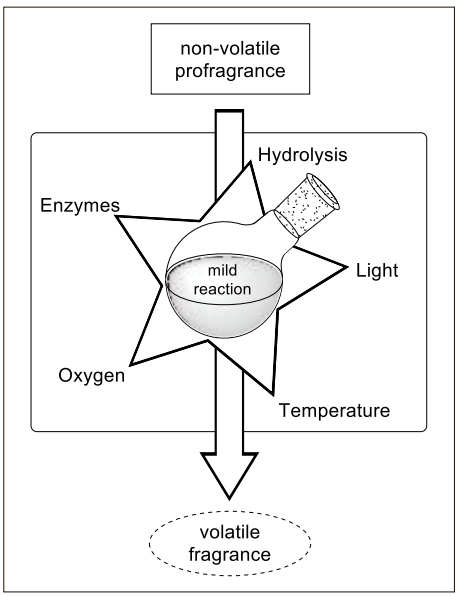
1. Introduction

Volatile compounds readily evaporate from various surfaces and travel through the air to reach their target. They are characterised by relatively low molecular weights, which at the same time limit the long-lastingness of their diffusion in the air. To release volatile biomolecules such as fragrances, pheromones and other signalling compounds,[1] nature uses precursors, such as glycosides,[2] which are stored and transported in plants as non-volatile conjugates and cleaved by an enzymatic mechanism to liberate the volatile part.

Because of their pleasant smell, many natural volatile compounds are found in the palette of the perfumer, a series that has been completed with the addition of synthetic molecules. Perfumes are composed of individual fragrances with different volatilities and used in fine perfumery, as well as in almost all body care or household products. The performance of these products is often judged by the duration of fragrance perception, and the prolongation of the olfactive impact of fragrances has thus become an important research area in the flavour and fragrance industry. Inspired by natural precursors, researchers have developed and evaluated numerous profragrances and properfumes in functional perfumery.[3,4] For these compounds to perform in application, the covalent bond that links the fragrance to its substrate must be cleaved under environmental conditions found in everyday life and thus has to rely on mild reactions using enzymes (as from micro-organisms), hydrolysis (such as the result of a change of pH), light (in particular ambient daylight), oxidation (with oxygen from the air), (moderate) temperature changes or a combination thereof (Scheme 1).[4]

In analogy to the development of prodrugs in the pharmaceutical industry,[5] profragrances were expected to constitute a complementary alternative to encapsu-



Scheme 1. Concept for the controlled release of volatile fragrances from non-volatile profragrances using mild organic reaction conditions.

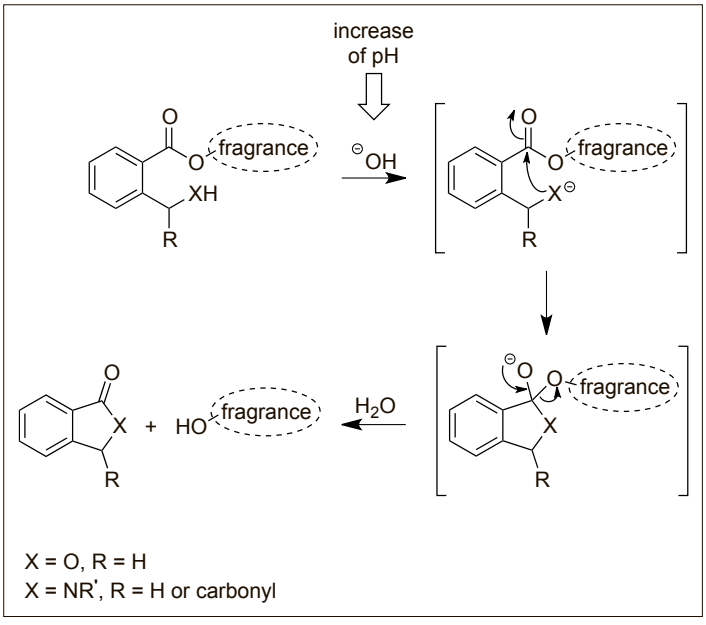
lation techniques. However, because of a series of particularities related to the volatility of fragrances and the fact that they have to evaporate from a surface and diffuse through the air to be smelled, prodrug technologies cannot easily be transferred to the delivery of perfumery compounds. As the general concepts and strategies applied to the successful development of profragrances have been reviewed in the past,[4] the present report highlights profragrance activities from my own laboratory during the last 20 years by focusing on some aspects of hydrolytically cleavable and light-sensitive fragrance delivery systems.

2. Hydrolytically Cleavable Profragrances

Similar to enzymatic systems, where the efficiency of a reaction often depends on the presence of specific functional groups in close proximity to the substrate to be formed or cleaved, intramolecular reaction pathways have been applied to break chemical bonds of suitably designed precursors. This principle, known as neighbouring group participation or intramolecular catalysis,[6] had already been investigated for the design of prodrugs.[7] In analogy to this concept, *ortho*-substituted benzoates, maleates or succinates have been evaluated for the controlled release of fragrance alcohols by intramolecular cyclisation using a nucleophilic neighbouring group (X), which is generated *in situ*, for example by a change in pH from acidic to neutral or slightly alkaline conditions (Scheme 2).[8]

It has been demonstrated that the rates of hydrolysis depend on the structure of the leaving alcohol (esters of primary alcohols hydrolysed faster than those of tertiary alcohols), on the precursor skeleton and on the structure of the intramolecularly attacking nucleophile.[8] The values represented in Fig. 1 for the hydrolysis of geranyl esters **1**–**8** show that, depending on the precursor skeleton, the rates for the release of geraniol span several orders of magnitude. The variation of the precursor structure thus allowed adaptation of the delivery system to the required release rate in the targeted application.

2-Carbamoylbenzoates were found to be particularly suitable for the release of tertiary alcohols,[8] which are in general poor leaving groups. Furthermore, their ease of preparation facilitated the functionalisation of oligomers and polymers containing amino groups, which are interesting substrates to monitor the deposition of the delivery systems on various surfaces. HPLC allowed the precise measurement of the rate constants for the first and second step of cyclisation of various poly(propylene imine) oligomers.[8,9] Comparison of covalent bond cleavage from the surface of linear, comb-like poly(propylene imine) stylomers (**9**, Fig. 2) and their corresponding spherical, globular dendrimers (**10**) showed that the polarity of the conjugates, and thus their solubility in the aqueous reaction medium, has a stronger impact on hydrolysis rates than the size (generation) or shape (linear or spherical) of the macromolecules.[9] For example, oligomers with five 2-carbamoylbenzoate units have been found to display typical polymeric characteristics. Furthermore, slight structural modifications in close proximity to the release unit, in particular the presence of residues with catalytic activity, have a strong influence on the release efficiency of the active molecules.[9] The findings using 2-carbamoylbenzoate functionalised stylomers and dendrimers as model compounds for polymers led to a fundamental understanding of how macromolecular structures influence fragrance release, and these results were consequently used for the design of profragrances grafted onto different commercially available polymer backbones.[10]



Scheme 2. General principle for the controlled release of fragrance alcohols by neighbouring group participation of *ortho*-substituted benzoates.[8]

Besides release efficiency, the stability of the precursors during storage is one of the most important criteria for the successful commercialisation of profragrance technologies.[4] In many cases, the efficient decomposition of the precursor under mild environmental conditions is incompatible with high product stability during storage and vice versa. In particular, if the precursor is kept in the presence of the trigger – which is the case for hydrolytically labile profragrances in water-based consumer products – only a compromise between precursor stability and efficient fragrance release can usually be achieved.

Inspired by recent developments in dynamic combinatorial/covalent chemistry,[11] we investigated the *in situ* generation of profragrances as an equilibrium of reversible reactions, so-called dynamic mixtures, to possibly circumvent product stability problems.[12,13] As long as the individual ingredients of the dynamic mixture are stable themselves, the proportion of the profragrance in equilibrium depends only on external parameters (such as concentration, temperature, pH or humidity, the presence of surfactant, *etc.*). A shift in equilibrium can always be corrected by resubmitting the product to the original conditions.

The reversibility of the formation and hydrolysis of hydrazones has previously been used in combinatorial chemistry for the generation of dynamic libraries for drug discovery or ligand identification.[11,14] In contrast to pharmaceutical applications where the condensation product of the reaction 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 in order to recover the active molecules from the transient condensation products.[12]

In this context, we explored the reversible formation of hydrazones[15] and of aminals[16] as chemical fragrance delivery systems. In aqueous solution, these reactions are reversible and reach an equilibrium consisting of a mixture of the unreacted hydrazine or diamine derivative and the unmodified carbonyl compound, together with the corresponding hydrazone or aminal condensation products (Scheme 3).

Adding a hydrazine or diamine derivative to a mixture of several fragrance aldehydes and ketones in the presence of water, for example in a fabric softener formula-

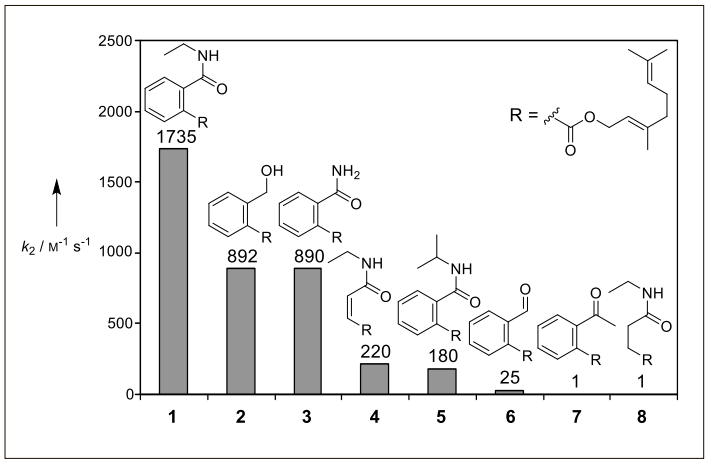


Fig. 1. Comparison of the second-order rate constants k_2 (in [M^{-1} s^{-1}]) obtained for the alkaline hydrolysis of geranyl esters **1**–**8**. Reprinted with permission from ref. [8a], copyright Wiley-VHCA, 2003.

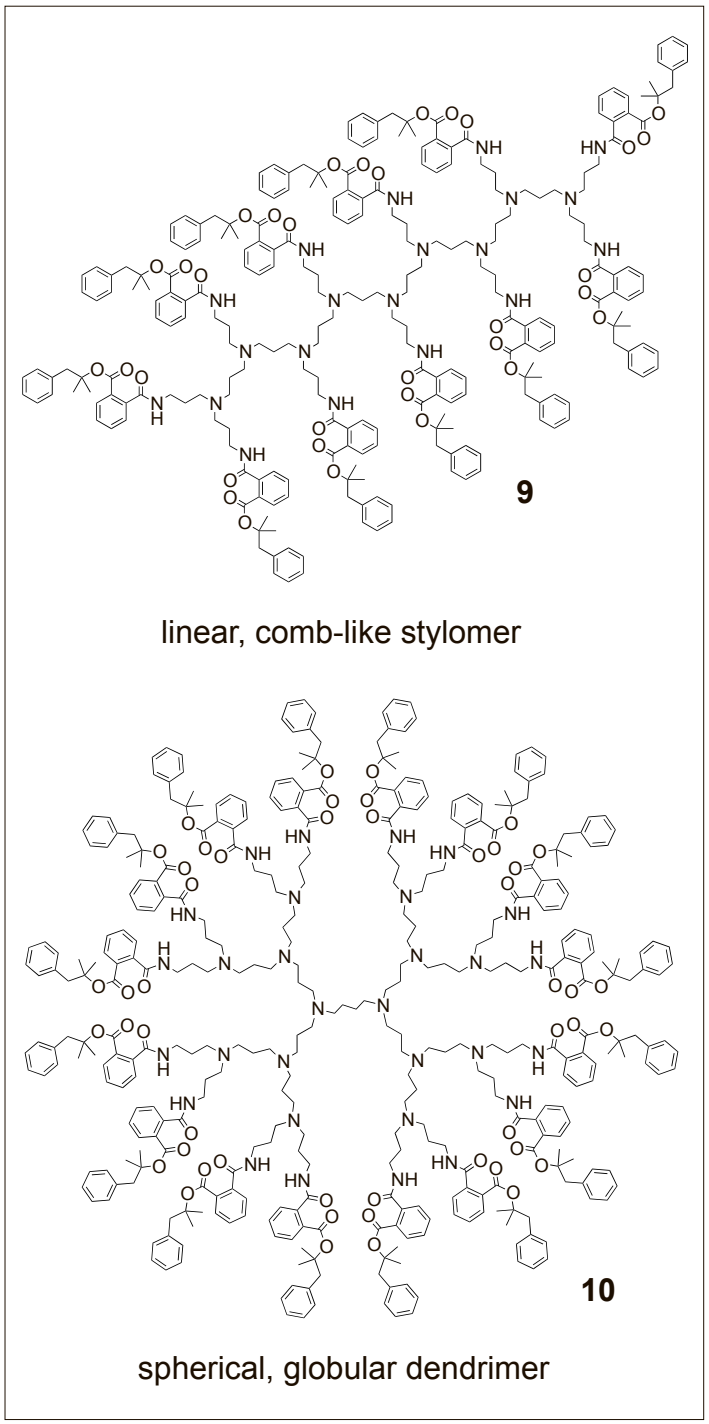


Fig. 2. Structures of linear, comb-like poly(propylene imine) stylomers (**9**) and their corresponding spherical, globular dendrimers (**10**) prepared for the controlled release of tertiary alcohols by pH-dependent stepwise cyclisation of the 2-carbamoylbenzoate moieties at their surfaces.[9]

tion, results in the generation of a dynamic mixture.[15,16] A multitude of profragrances is formed spontaneously, 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 regeneration of the starting hydrazine or diamine derivative.[12,13]

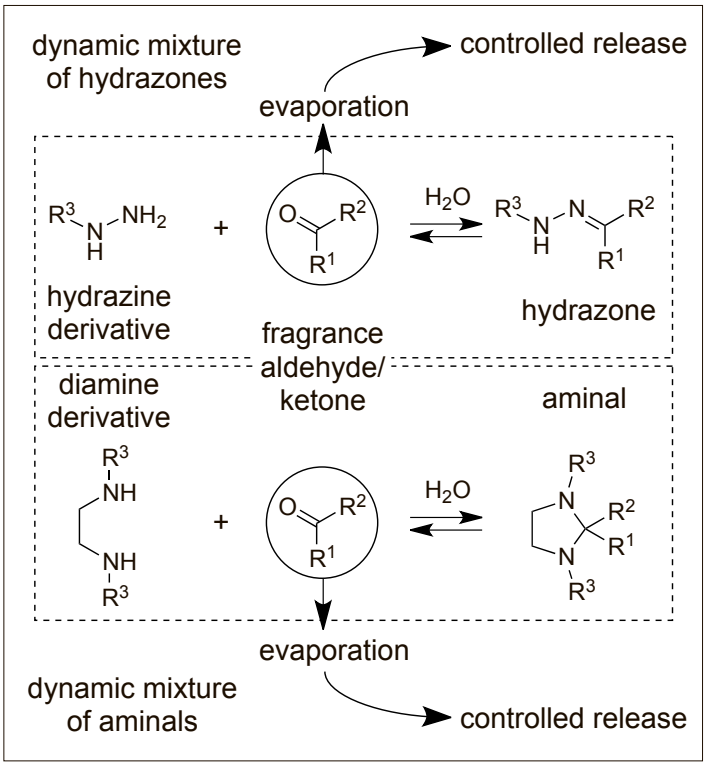
Dynamic headspace analysis on dry cotton showed that the presence of a hydrazine (**11**) or diamine derivative (**12**) significantly increased the headspace concentrations of the different carbonyl compounds in comparison to the reference sample without hydrazine or diamine (Fig. 3).[15,16] The release of the volatiles was found to be efficient for fragrances with high vapour pressures and low water solubility. Furthermore, a particular long-lasting effect was generally obtained. The fact that all carbonyl compounds in a mixture can be affected by the presence of a hydrazine or diamine derivative makes dynamic mixtures particularly powerful for the controlled release of fragrances. The use of dynamic mixtures to control the release of fragrances is an illustrative example for the practical applicability of concepts developed in competitive and interdisciplinary up-to-date research.[13]

3. Light-induced Profragrance Cleavage

As fragrance evaporation takes place on surfaces that are generally exposed to ambient daylight, photoresponsive profragrances seem to be ideal delivery systems for the controlled release of volatiles.[4,17–19] For efficient release under ambient conditions, light-activated delivery systems, so-called photocages, have to respond to the relatively low light intensities of normal daylight and to work in the presence of oxygen in polar solutions, typically in water. This is not the case for every photochemical reaction and, in particular, the presence of oxygen may be critical.[17] A reaction fulfilling these requirements is the Norrish type II photofragmentation[19,20] of alkyl or aryl 2-oxoacetates (α-keto esters)[21–23] depicted in Scheme 4.

Upon irradiation with UVA light (at *ca.* 350–370 nm) γ-hydrogen abstraction forms an intermediate 1,4-biradical, which decomposes to yield the final reaction products.[21–23] Depending on whether the reaction is performed in the absence or presence of oxygen, CO or CO_2 is generated. Corresponding aldehydes or ketones have usually been obtained in good yields upon irradiation with a xenon lamp or outdoor sunlight. 2-Cyclohexyl-2-oxoacetates and 2-oxo-2-phenylacetates have been identi-

Scheme 3. General concept for the reversible formation and hydrolysis of hydrazones and aminals for the controlled release of fragrance aldehydes and ketones.[15,16]



fied as the most suitable precursors for the desired perfumery applications.[23,24]

Dynamic headspace analysis under realistic application conditions has been shown to give rise to increased long-lastingness of the fragrance perception compared to the corresponding unmodified fragrance reference.[24] Furthermore, fragrance release was observed to generally depend on light intensity, as shown for the exposure of **13**, present in an aqueous all-purpose cleaner film, to variable outdoor sunlight (Scheme 5). During a day, the light intensity typically increases in the morning to reach a maximum value around noon, and then decreases again in the afternoon. The data depicted in Scheme 5 has been recorded between 10 a.m. and about 4 p.m. on a sunny day. As one can see, the measured headspace concentrations of the released fragrance aldehyde (citronellal) correlated well with the recorded light intensity.[24] Furthermore, they were far above the human olfactory threshold level of citronellal; the compound could thus be easily smelled during the experiment.

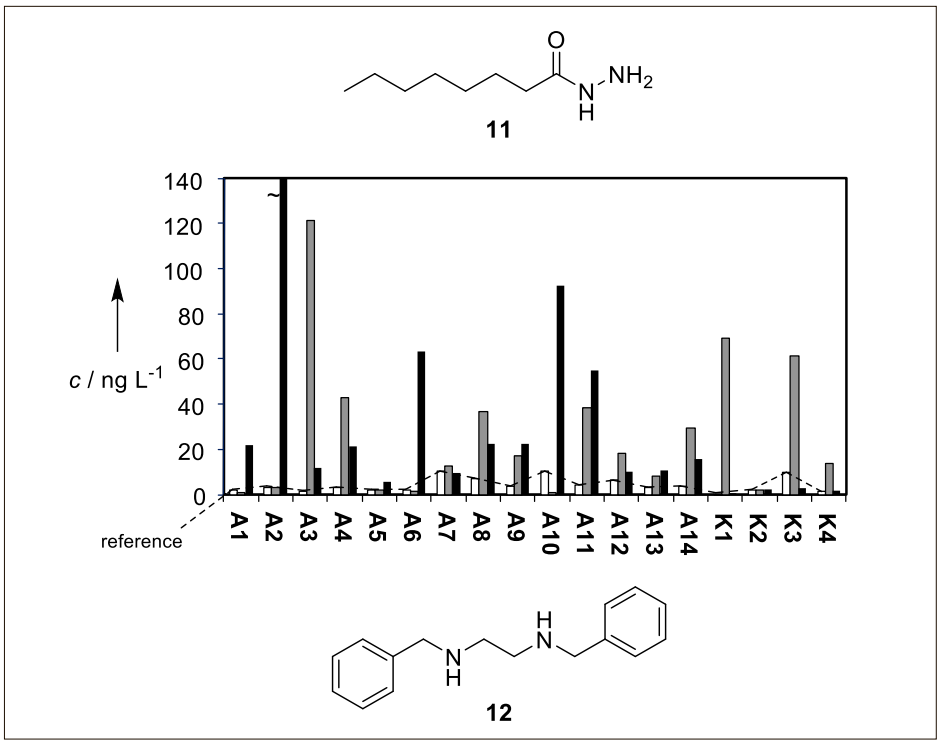


Fig. 3. Comparison of the dynamic headspace concentrations measured on dry cotton for the evaporation of a mixture of 14 aldehydes (**A1**–**A14**) and 4 ketones (**K1**–**K4**) in the presence of hydrazine **11** (grey bars) or diamine **12** (black bars) with respect to samples measured in their absence (reference sample, white bars and dotted line).[15,16]

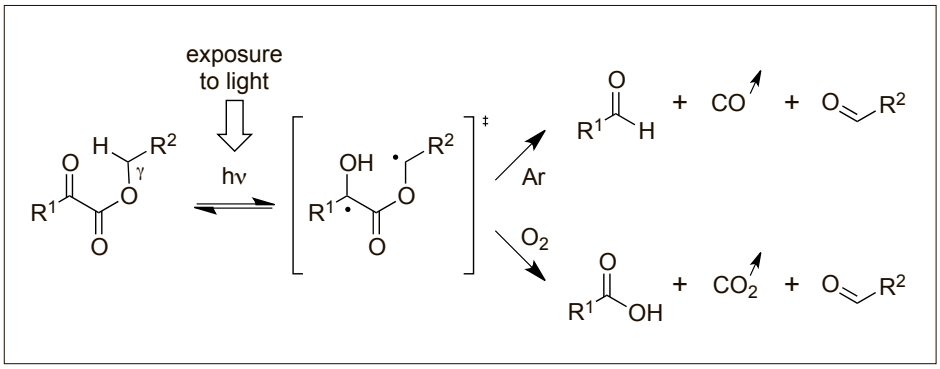
Norrish type II photofragmentations of 2-oxoacetates are thus suitable to control the release of fragrances under realistic perfumery application conditions. The studies showed that outdoor sunlight – one of the main energy sources for biological processes – is sufficient for the desired fragrance delivery and that the desired photoreaction proceeds in a polar environment while tolerating the presence of oxygen.[23,24]

Despite their strong performance when exposed to daylight, 2-oxoacetates are partially hydrolysed when stored in an aqueous environment at extreme pH. For their use in aqueous product formulations, we compared two alternative concepts as outlined in Scheme 6. In a first approach, 2-oxo-2-(4-vinylphenyl)oxoacetates were synthesised, which could then be copolymerised into latex nanoparticles, with the polymeric environment stabilising the labile ester bond. The other strategy consisted in the encapsulation of 2-oxoacetate profragrances into core-shell microcapsules.[25]

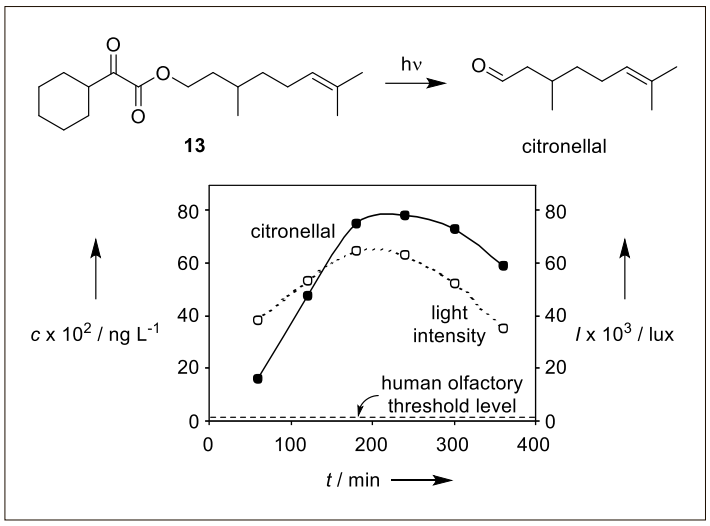
In both cases, no hydrolysis of the ester bond was observed, even after prolonged standing of different samples in an aqueous environment. At the same time, the light-induced release of the fragrances was not hindered.[25] During these studies, we have seen that, surprisingly, some of the 2-oxoacetate-containing microcapsules showed rapid fragrance release when exposed to UVA irradiation.[26] Photolysis of encapsulated and non-encapsulated 2-oxoacetates resulted in a closely related fragrance release profile, suggesting that the presence of the capsule wall had almost no effect on the retention of the fragrance.

This behaviour could be explained by a rapid expansion or burst of the capsule wall as a consequence of gas overpressure inside the capsule following the light-induced generation of CO and CO_2 as side products of the Norrish type II photofragmentation mentioned earlier (Scheme 7).[26] The formation of the two gases has repeatedly been noted in the literature,[21] but little or no advantage has so far been taken from this observation.

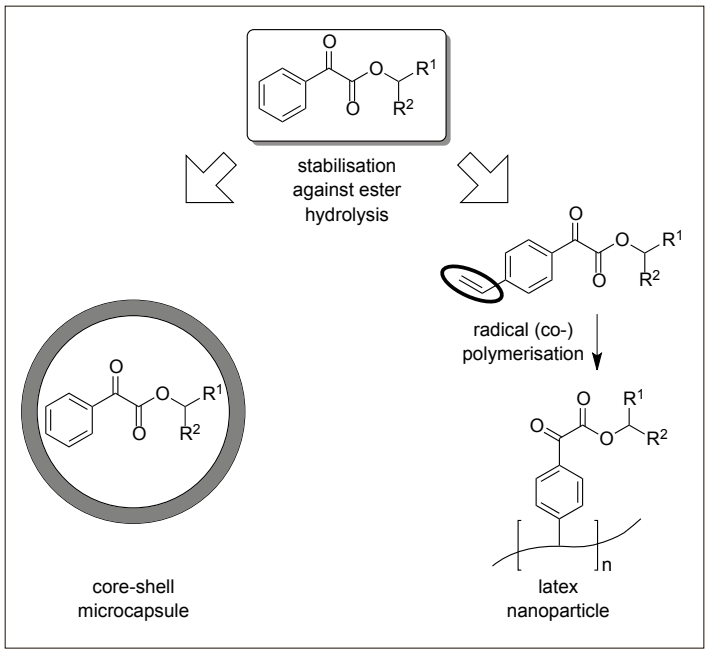
Dynamic headspace analysis finally confirmed the light-induced formation of CO and CO_2, together with the desired fragrance release. The formation of gas bubbles was visualised by optical microscopy (Fig. 4, black arrow), which also demonstrated the cleavage of the capsule wall ac-



Scheme 4. Norrish type II photoreaction of 2-oxoacetates in the presence or absence of oxygen.[21]



Scheme 5. Dynamic headspace analysis of the light-dependent release of citronellal from precursor **13** in an all-purpose cleaner film exposed to outdoor sunlight.[24] The solid line represents the concentration of fragrance released into the headspace; the dotted line shows the evolution of daylight intensity with a maximum value around noon.



Scheme 6. Stabilisation of 2-oxo-2-phenylacetates against hydrolysis by encapsulation into core-shell microcapsules or by polymerisation into latex nanoparticles.[25]

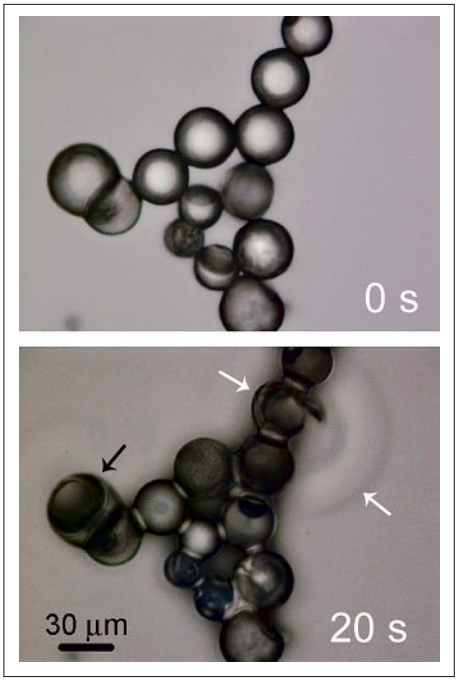
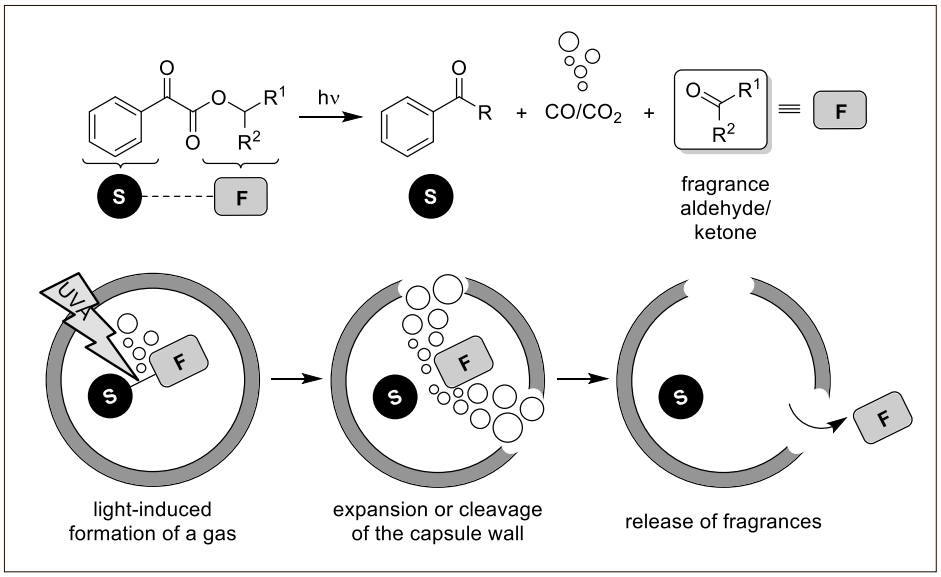


Fig. 4. Optical microscopy images for the photoirradiation of microcapsules containing a photolabile 2-oxo-2-phenylacetate and a co-encapsulated fragrance molecule before and after irradiation with UVA light for 20 s. The black arrow shows the formation of a gas bubble; the white arrows demonstrate the cleavage of a capsule's shell and the leakage of the oil phase. Reprinted (in part) with permission from ref. [26], copyright Wiley-VCH, 2015.

companied by leakage of the oil phase out of the capsule (white arrows).[26] This now allows the light-induced release of any fragrance molecule co-encapsulated with any gas-generating 2-oxoacetate from core-shell microcapsules. The simplicity of the concept makes it a valuable alternative to the so far existing light-responsive delivery systems, which are typically based on the use of photocleavable or photoisomerisable moieties built into the capsule wall. It is likely that this concept can be applied to a broad variety of structures other than 2-oxoacetates, as long as they are able to generate a gas on exposure to light, and that the general concept will be of interest for the light-induced release of bioactive compounds in other areas of life sciences.

4. Conclusions

Mild environmental conditions, such as hydrolysis at different pH, reversible reactions or the action of light, allow an efficient control of the evaporation of volatile organic molecules by covalent bond cleavage from suitably designed precursors. Profragrance development is an interdisciplinary endeavour that covers organic, supramolecular, physical and analytical chemistry, as well as various aspects of materials science. On the one hand, the successful development of profragrances requires insight into mechanistic aspects of organic reactions to understand and suppress the formation of side products. On the other hand, issues of reaction kinetics, product formulations, stability, deposition on target surfaces and many others need to be addressed. In particular, the work on light-induced degradation of 2-oxoacetates demonstrates the interdisciplinary aspect of the research area, spanning from classic profragrances to bursting capsules. The fundamental work on profragrances as outlined above has contributed to the practical deployment of this technique, which today represents an important delivery technology for the release of fragrances in functional perfumery and which is complementary to encapsulation systems.



Scheme 7. UVA-induced formation of a gas from encapsulated photolabile 2-oxo-2-phenylacetates and simultaneous formation of a fragrance molecule.[26]

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