COMMUNICATION

Controlled release of perfumery alcohols by alkaline hydrolysis of 2-formyl- and 2-acetylbenzoates and their corresponding phthalides

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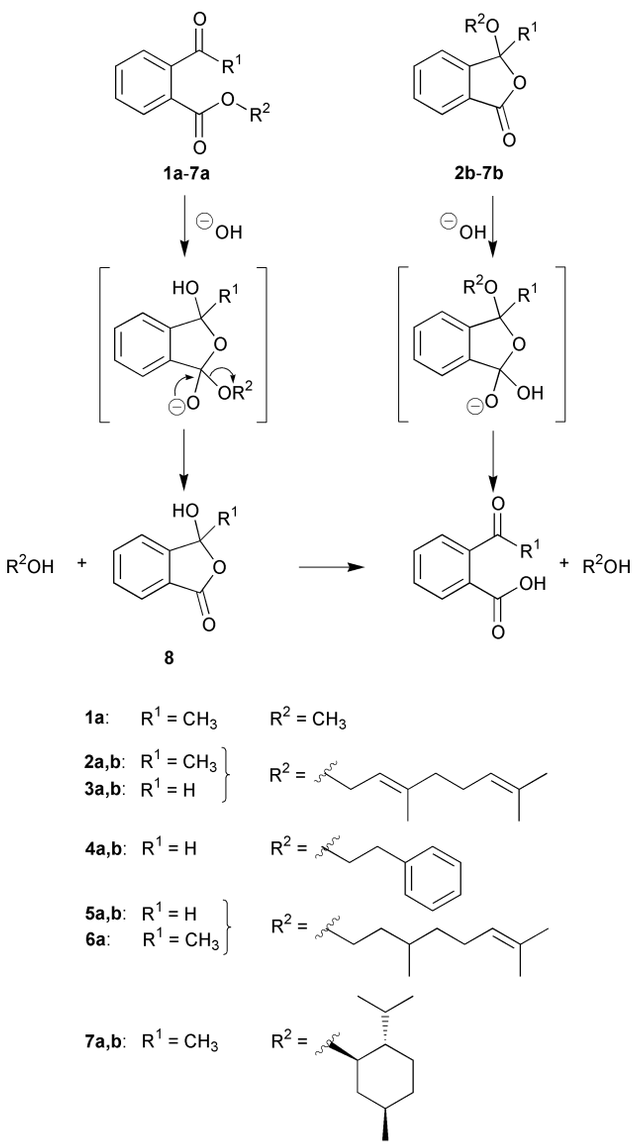
The 2-formyl- and 2-acetylbenzoates of fragrance alcohols and their corresponding pseudo-esters (phthalides) are suitable precursors for the controlled release of fragrances by alkaline hydrolysis; the rate of benzoate hydrolysis depends on the structure of the alcohol released.

To increase the performance of consumer products, and, in particular to prolong the perception of volatile molecules such as flavours or fragrances, the development of suitable delivery systems for functional perfumery applications such as shampoos, creams, soaps, fabric softeners or detergent powders is becoming an increasingly important research area in the flavour and fragrance industry.[1] Most of the delivery systems described so far are based on the release of active compounds from an encapsulating matrix, by diffusion out of the matrix or by destruction of the capsules. An alternative to encapsulation consists of the preparation of suitable precursors that release the active material by a chemical reaction in the targeted application.[2] We herein describe the preparation of a series of 2-formyl- and 2-acetylbenzoates, as well as their cyclic pseudo-esters (phthalides), for the controlled release of perfumery alcohols in alkaline media. The release mechanism of the benzoates in basic solution is based on the hydration of the carbonyl group followed by intramolecular nucleophilic attack (neighbouring group participation)[3] to form a lactone (which then opens to the carboxylate of the corresponding acid) and the desired perfumery alcohol, with the hydroxide ion addition[4] or the cyclisation[5] being the rate determining steps. In the case of the pseudo-esters, the rate determining step is the addition of hydroxide to the ester carbonyl group.[6,7] Rapid ring opening then gives the anion of the corresponding carboxylic acid together with the fragrance alcohol (Scheme 1).

Several attempts to synthesise 2-substituted benzoates from the corresponding benzoic acids, *via* their acid chlorides[8] and a perfumery alcohol, were unsuccessful, presumably due to ring–chain tautomerism of the carboxylic acid.[9] Methyl 2-acetylbenzoate (**1a**) (Scheme 1) was successfully obtained by reaction of 2-acetylbenzoic acid with diazomethane.[10] Transesterification with geraniol using sodium methoxide in cyclohexanol resulted in a *ca.* 1 : 1 mixture of benzoate **2a** and pseudo-ester **2b**. Formyl- and acetylbenzoates **2a**–**7a** (Scheme 1) were finally synthesised from their corresponding acids using 1,3-dicyclohexylcarbodiimide (DCC) with 4-dimethylaminopyridine (DMAP) in dichloromethane.†[11,12] Whereas phthalides **3b**–**5b** were obtained as side products in the DCC coupling reaction of 2-formylbenzoic acid, the formation of 3-methylphthalides in the reaction with 2-acetylbenzoic acid was not observed. All compounds were stable and could be isolated in their pure state. No evidence for an equilibration between the corresponding ring–chain tautomers was obtained under the conditions described in this study. Interestingly, the reported synthesis of **7a** *via* the acid catalysed esterification of 2-acetylbenzoic acid with (−)-menthol using HCl,[13] could not be reproduced: following the published procedure we obtained pseudo-ester **7b** as a diastereoisomeric mixture.



Scheme 1

The kinetics for the alkaline hydrolysis of the methyl or phenyl esters of 2-formyl- or 2-acetylbenzoates[4,5,12,14,15] and their pseudo-esters[6,15] have been investigated by different research groups. In these studies the dependence of the rate of hydrolysis with respect to substitution on either the carbonyl function or the aromatic ring was analysed in detail.[5,6,12] However, the influence of the leaving alcohol on the rate constants of the hydrolysis, which is crucial for the targeted application in functional perfumery, has not been studied extensively. Phenyl 2-acetylbenzoates were reported to hydrolyse *ca.* 1.3 times faster

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Table 1 Measured rate constants k_0 for the alkaline hydrolysis of 2-formyl- and 2-acetylbenzoates **1a**–**7a** and their pseudo-esters **3b**–**7b** in water–acetonitrile 2 : 1 at 20 °C. All numbers are average values of at least two experiments

Compound	$k_0 \times 10^5/s^{-1}$	pH	Compound	$k_0 \times 10^5/s^{-1}$
1a	12.7	10.47		
2a	3.98	10.47		
	38.2	11.54		
3a	108	10.47	**3b**	0.839
		11.54		7.17
4a	315	10.47	**4b**	0.940
		11.54		9.79
5a	30.0	10.47	**5b**	0.865
		11.54		6.62
6a	2.50	10.47		
	25.6	11.54		
7a		10.47	**7b**	0.153
	2.89	11.54		

than the corresponding methyl esters,[12] and the influence of the alcohol released in the hydrolysis of the pseudo-esters of 2-benzoylbenzoates was found to be poor.[7] In this work, the rate constants of precursors **1**–**7** were determined in buffered solutions of water–acetonitrile 2 : 1 at 20 °C. The reaction solutions were injected at constant time intervals into a high performance liquid chromatography (HPLC) apparatus and eluted on a reversed phase column with water–acetonitrile.‡ Due to the fact that the hydroxide concentration was held constant by the buffer, the second order rate expression $k_2[OH^-][precursor]$ can be reduced to the first order expression $k_0[precursor]$.[5] Plotting the logarithm of the surface area quotients (A_t/A_0) of the benzoates or phthalides against time gives a straight line with good correlation coefficients (>0.99) for all the measurements, thus justifying the general assumption of first order kinetics. The rates of hydrolysis were found to slightly deviate from proportionality to the hydroxide ion concentration under the conditions described in this work. However, for our purposes, the direct comparison of the measured rate constants (k_0) at the same pH was sufficient. The results obtained for the release of different perfumery alcohols are summarised in Table 1. UV spectra measured after complete transformation showed that the reaction proceeds completely to the acid in the open form, and the formation of the ring–chain tautomeric phthalide **8** as reaction intermediate was not observed. Direct comparison of the rate constants (k_0) measured for methyl 2-acetylbenzoate (**1a**) in this study with those reported in water–1,4-dioxane[5] shows that our reaction rates (determined by HPLC as well as by UV spectroscopy) are *ca*. ten times slower than the literature values.[16] The hydrolysis of citronellyl 2-formylbenzoate (**5a**) is about ten times faster than that of the corresponding 2-acetyl derivative **6a**, whereas geranyl 2-formylbenzoate (**3a**) hydrolyses *ca*. 25 times faster than its 2-acetyl analogue **2a**. Interestingly the rate constants are also very strongly dependent on the structure of the alcohol released during the hydrolysis. Comparison of menthyl 2-acetylbenzoate (**7a**), which liberates a secondary alcohol, with primary alcohol derivatives **6a** or **2a**, shows that, in the last two cases, the rate of ester hydrolysis increases roughly by factors of 10 and 15, respectively. Moreover, benzoates of allylic primary alcohols (geraniol) are hydrolysed twice as fast as their homologous saturated alcohols (citronellol). This is not the case for phthalides **3b**, **4b** and **5b**, where all the measured rate constants are of the same order of magnitude. Doubling the buffer concentration at the same pH did not influence the rate of hydrolysis of the benzoates within the experimental error. In the case of the phthalides, however, a slight decrease of the rate constants (by *ca.* 20% for **5b**) was observed at higher buffer concentrations, a fact that indicates the participation of the buffer components in the reaction pathway.

Our results suggest that the structure of the leaving alcohol is important in the rate determining step of the alkaline hydrolysis of the benzoates, but not in the case of the phthalide derivatives. Both the benzoates **1a**–**7a** and phthalides **2b**–**7b** were found to liberate the desired perfumery alcohols, and can thus be used as delivery systems for the controlled release of fragrances in functional perfumery.[17] Due to their broad range of different rate constants, mixtures of benzoates and phthalides such as **3a** and **3b** may well be efficient for providing a long lasting effect of odour perception in perfumery applications; this aspect is currently under investigation.

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Notes and references

† *Representative experimental procedure*. A solution of 7.50 g (50.0 mmol) of 2-formylbenzoic acid, 4.89 g (40.0 mmol) of DMAP and 15.42 g (100.0 mmol) of geraniol in CH_2Cl_2 (75 ml) was cooled in an ice-bath prior to the addition, over 15 min, of a solution of 11.37 g (55.0 mmol) of DCC in CH_2Cl_2 (25 ml). The reaction mixture was stirred for 15 min at 0 °C, then at 20 °C for 48 h. The precipitate formed in the reaction was filtered off and the filtrate washed with HCl (10%, 2×), a saturated solution of Na_2CO_3 (2×) and water (2×, pH ≈ 7). The organic layer was dried (Na_2SO_4), concentrated and chromatographed (SiO_2, heptane–ether 8 : 2) to give 2.55 g (22%) of **3a** and 4.36 g (38%) of **3b**. Full spectroscopic data have been obtained for all new compounds.

‡ *Procedure for the hydrolysis experiments*. All samples were thermostatted at 20 °C. The pH values of the buffer solutions in water–acetonitrile 2 : 1 were measured (on a Mettler Toledo MP220 instrument with an InLab 410 Ag/AgCl glass electrode) to be 10.47 ± 0.01 (borate) or 11.54 ± 0.02 (phosphate–bicarbonate). Compounds **1**–**7** (35 to 45 mg) were dissolved in 25 ml of acetonitrile and 0.2 ml of this solution were added to 1.0 ml of a buffer solution in water–acetonitrile 4 : 1. The mixture was immediately injected in a HPLC apparatus ($t = 0$), eluted at 1 ml min^{-1} on a reversed phase column with a mixture of water–acetonitrile containing 0.1% of TFA and analysed at $\lambda = 254$ nm. Most of the chromatograms were recorded on a Macherey-Nagel, Nucleosil 100-5 C18 column (250 × 4 mm id) using a water–acetonitrile gradient (70 : 30 to 20 : 80 over 20 min) and re-injected (20 μl) every 35 or 70 min (20 times). The kinetics of compounds **2a** and **6a** (at pH 11.54) as well as **3a** and **4a** were measured on a Merck Chromolith SpeedROD RP-C18e column (50 × 4.6 mm id) by isocratic elution with water–acetonitrile 3 : 7 (**2a**, **3a** and **6a**) or 2 : 3 (**4a**). The samples (10 μl) were re-injected every 5.3 or 4.3 min, respectively (12–20 times). A_t = surface area at time t, A_0 = surface area at $t = 0$.

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