Stabilized Hemiacetal Complexes as Precursors for the Controlled Release of Bioactive Volatile Alcohols

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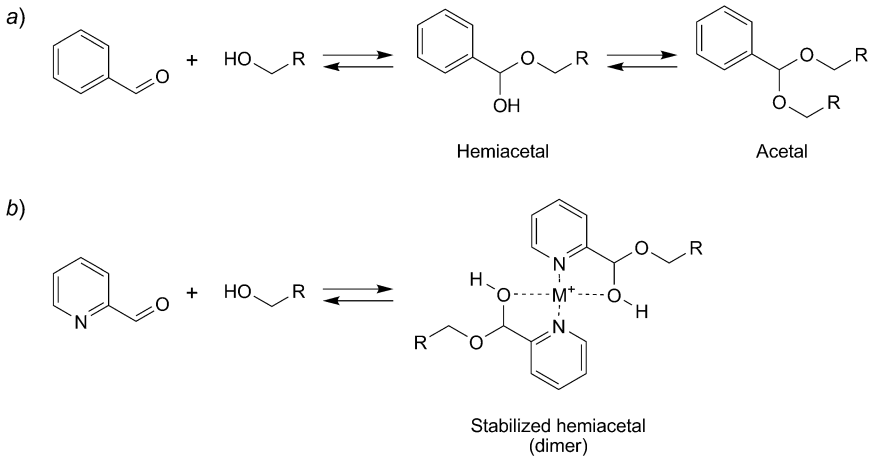
Hemiacetals of pyridine-2-carbaldehyde derivatives and volatile alcohols can be stabilized in organic solution in the presence of protons or different metal cations. Despite the inherent instability of hemiacetals in H_2O, stabilizing them with zinc(II) triflate and adding them to a cationic surfactant formulation resulted in the slow release of the alcohol from cotton surfaces being treated with the hemiacetal complex. Stabilized hemiacetals might thus be suitable delivery systems of bioactive volatiles by rapid hydrolysis in H_2O-based media.

Introduction. – Bioactive volatile compounds play an important role as flavors and fragrances in our everyday life [1]. As a consequence of their high vapor pressures, volatiles rapidly evaporate from various surfaces, which limits their duration of perception. The development of fragrance precursors, so-called profragrances, which release the volatile compound by covalent-bond cleavage under mild environmental conditions, has recently been described as an interesting possibility to increase the long-lasting character of fragrance performance in consumer products [2].

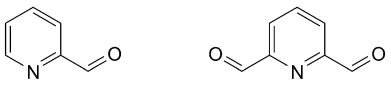
Acetals or ketals, sometimes as a mixture with hemiacetals, have been obtained by the reaction of alcohols with carbonyl derivatives and investigated as hydrolytically cleavable profragrances to control the release of alcohols and/or carbonyl compounds [2][3]. Generally, acetals or ketals (in particular, cyclic ones) are relatively stable under very mild reaction conditions and are, therefore, only of limited interest for the release of volatiles in practical applications. The hydrolysis of acetals and ketals is generally acid catalyzed [4] and proceeds *via* the formation of an unstable hemiacetal, which is formed in small amounts and is thus usually difficult to isolate (*Scheme*, *a*) [5][6]. On the other hand, if hemiacetals could be generated in sufficient quantities by suitable stabilization in the reaction medium, their inherent instability should allow fast release kinetics, resulting in the rapid evaporation of the corresponding volatile compounds. Some acyclic hemiacetals have been generated or isolated under various conditions: for example, from electron-withdrawing aldehydes and small alcohols [7], in the solid state by melting a mixture of fatty alcohols and aldehydes [8] or by benefiting from particularly strong intramolecular H-bonding [9], in ionic and molecular liquids [10], as methyl hemiacetals of some tripeptide aldehydes [11], as polymer-bound systems in a sterically demanding environment [12], or as a hydrolyti-

cally cleavable moiety for polymer degradation [13]. They have also been stabilized as inclusion complexes by surrounding them with suitably designed cavitands [14]. Hemiacetals formed by reaction of pyridine-2-carbonyl derivatives [15] with different alcohols have successfully been stabilized by protonation or by metal cation coordination with the electron-donating N-atom of the pyridine moiety and the OH group of the hemiacetal (*Scheme*, *b*) [10][16][17]. They may thus also be implemented in the context of dynamic covalent chemistry [17].

Scheme. *Reversible Formation of Hemiacetals and Acetals* (*a*) *and of Stabilized Hemiacetal Metal Cation Complexes* (*b*)



Stabilized hemiacetals of pyridine-2-carbaldehyde (**1**; *Fig. 1*) or pyridine-2,6-dicarbaldehyde (**2**) with various primary, secondary, or tertiary alcohols were obtained in equilibrium with the corresponding free aldehyde and alcohols in yields of up to 80%, whereas, in the absence of a stabilizing proton (*e.g.*, from CF_3COOH (TFA)) or metal cation (such as Zn^{2+} or Pb^{2+}), considerable amounts of hemiacetals were formed only when a large excess of alcohol was used [17]. The optimum ratio between the ligand and the stabilizing cation was determined to be 2 : 1 (for Zn^{2+}) or 1 : 1 (for Pb^{2+}). As expected, primary alcohols were found to be more reactive than secondary or tertiary alcohols, whereas phenols did not react at all [17].



1 **2**

Fig. 1. *Carbonyl derivatives allowing the preparation of stabilized hemiacetals*

Encouraged by these findings, we were interested to see whether this concept might apply to the release of fragrance alcohols under practical application conditions in perfumery[1]). With lead complexes being undesirable as constituents in consumer articles, we focused our interest on the study of zinc complexes.

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[1]) Parts of this publication are the subject of a patent application [18].

Results and Discussion. – *Formation of Stabilized Hemiacetals in Solution*. The formation of stabilized hemiacetals was investigated by ^{1}H-NMR spectroscopy with commercially available aldehydes **1** and **2**, and a series of primary fragrance alcohols, notably (*R*)-3,7-dimethyloct-6-en-1-ol (citronellol; **A**), (*E*)-3,7-dimethylocta-2,6-dien-1-ol (geraniol; **B**), 2-phenylethanol (**C**), and (*Z*)-hex-3-en-1-ol (**D**). In general, the aldehyde concentration was fixed at 0.15 mol l^{-1}, while the concentrations of the alcohol and the stabilizing proton or metal cation were adjusted with respect to the concentration of the aldehyde. In a typical experiment, 0.9 mmol of the aldehyde, a mol-equiv. of fragrance alcohol, and 0.5 mol-equiv. of stabilizing salt were weighed into MeCN and pipetted into an NMR tube. After mixing the compounds, the samples were left to stand overnight and analyzed the next day. The ^{1}H-NMR spectra were acquired with 320 scans, and quantitative data were calculated by integrating the signals of the H-atoms at the C-atom adjacent to the O-atom of the alcohol moiety for both the hemiacetal and the free alcohol in the compound mixture. The peaks were in general well separated; overlapping peaks were observed in only a few cases.

In a first set of experiments (carried out in $CDCl_3$), we determined the amount of non-stabilized hemiacetal formed by reaction of aldehydes **1** and **2**, with alcohols **A** and **B**, respectively, in the absence of stabilizing protons or metal cations. The data obtained for the different product distributions are compiled in *Table 1*.

As expected with equimolar amounts of alcohol, less than 10% of hemiacetal was obtained with aldehyde **1** (*Table 1*, *Entries 1* and *2*). In the case of aldehyde **2**, *ca*. 20–30% of mono-hemiacetal, but no bis-hemiacetal, was formed (*Entries 27* and *28*). Adding 3 mol-equiv. of TFA (with respect to the aldehyde) considerably increased the amount of hemiacetal detected in the mixture (*Entries 3–6*). In the case of geraniol (**B**), the solvent does not seem to play a major role for the formation of the hemiacetal. Comparable results were obtained with $CDCl_3$ or CD_3CN, whereas, in the case of citronellol (**A**) as the alcohol, about twice as much hemiacetal was formed when CD_3CN was used as the solvent.

As strongly acidic conditions are rarely encountered in practical applications, the stabilization of the hemiacetals by protic acids is only of limited interest. In our further investigations, we thus focused on the use of metal cations to stabilize the hemiacetals of fragrance alcohols. Tests were carried out with different fragrance alcohols by using 0.5 equiv. of zinc triflate ($Zn(CF_3SO_3)_2$, $Zn(OTf)_2$), or zinc chloride ($ZnCl_2$) as stabilizing salts in CD_3CN (*Entries 7–14*). Our data indicated that the nature of the anion seems to be important for the stabilization of the hemiacetal complexes. When $ZnCl_2$ was used, only about half as much of the hemiacetal complexes were formed as compared with the measurements carried out with $Zn(OTf)_2$ as the stabilizing salt.

Higher amounts of hemiacetals were also formed by using dicarbaldehyde **2** for the formation of the complexes. In the presence of $Zn(OTf)_2$, 77% of hemiacetal was formed with citronellol (**A**) in CD_3CN, while the formation of the corresponding bis-hemiacetal was not observed (*Entry 29*). 2-Oxoacetic acid also formed stabilized hemiacetals under the present conditions. Use of citronellol (**A**) as the fragrance alcohol and $Zn(OTf)_2$ as the stabilizing salt resulted in the formation of 66% of hemiacetal in CD_3CN. Adding 3 equiv. of TFA instead of 0.5 equiv. of $Zn(OTf)_2$ resulted in the formation of gels.

Table 1. *Amounts of Free Alcohol and Corresponding Hemiacetal Determined by ^{1}H-NMR in $CDCl_3$ or CD_3CN for an Equilibrated Mixture of Fragrance Alcohols* **A**–**D**, *and Aldehydes* **1** *and* **2** *in the Presence or Absence of TFA or Zn^{2+} Salts as Stabilizing Agents*

Entry	Aldehyde (solvent)	Equiv. of alcohol	Equiv. of TFA or stabilizing salt	Amount of remaining alcohol [%]	Amount of mono-hemi-acetal formed [%]	Amount of bis-hemi-acetal formed [%]
1	**1** ($CDCl_3$)	**A**: 1.0 equiv.	–	97	3	–
2		**B**: 1.0 equiv.	–	94	6	–
3	**1** ($CDCl_3$)	**A**: 1.0 equiv.	TFA: 3.0 equiv.	75	25	–
4		**B**: 1.0 equiv.	TFA: 3.0 equiv.	43	57	–
5	**1** (CD_3CN)	**A**: 1.0 equiv.	TFA: 3.0 equiv.	44	56	–
6		**B**: 1.0 equiv.	TFA: 3.0 equiv.	42	58	–
7	**1** (CD_3CN)	**A**: 1.0 equiv.	$Zn(OTf)_2$: 0.5 equiv.	61	39	–
8		**B**: 1.0 equiv.	$Zn(OTf)_2$: 0.5 equiv.	60	40	–
9		**C**: 1.0 equiv.	$Zn(OTf)_2$: 0.5 equiv.	49	51	–
10		**D**: 1.0 equiv.	$Zn(OTf)_2$: 0.5 equiv.	64	36	–
11	**1** (CD_3CN)	**A**: 1.0 equiv.	$ZnCl_2$: 0.5 equiv.	80	20	–
12		**B**: 1.0 equiv.	$ZnCl_2$: 0.5 equiv.	79	21	–
13		**C**: 1.0 equiv.	$ZnCl_2$: 0.5 equiv.	75	25	–
14		**D**: 1.0 equiv.	$ZnCl_2$: 0.5 equiv.	82	18	–
15	**1** (CD_3CN)	**B**: 1.0 equiv.	$Zn(OTf)_2$: 0.0 equiv.	97	3	–
16			$Zn(OTf)_2$: 0.2 equiv.	67	33	–
17			$Zn(OTf)_2$: 0.3 equiv.	57	43	–
18			$Zn(OTf)_2$: 0.5 equiv.	52	48	–
19			$Zn(OTf)_2$: 0.7 equiv.	49	51	–
20			$Zn(OTf)_2$: 1.0 equiv.	63	37	–
21	**1** (CD_3COCD_3)	**A**: 1.0 equiv.	$Zn(OTf)_2$: 0.5 equiv.	72	28	–
22		**B**: 1.0 equiv.	$Zn(OTf)_2$: 0.5 equiv.	60	40	–
23		**C**: 1.0 equiv.	$Zn(OTf)_2$: 0.5 equiv.	63	37	–
24		**D**: 1.0 equiv.	$Zn(OTf)_2$: 0.5 equiv.	66	34	–
25	**1** (CD_3CN/D_2O 2 : 1)	**A**: 1.0 equiv.	$Zn(OTf)_2$: 0.5 equiv.	97	3	–
26		**B**: 1.0 equiv.	$Zn(OTf)_2$: 0.5 equiv.	95	5	–
27	**2** ($CDCl_3$)	**A**: 2.0 equiv.	–	81	19	0
28		**B**: 2.0 equiv.	–	74	26	0
29	**2** (CD_3CN)	**A**: 2.0 equiv.	$Zn(OTf)_2$: 0.5 equiv.	23	77	0
30	**2** (CD_3CN)	**B**: 1.0 equiv.	$Zn(OTf)_2$: 0.0 equiv.	87	13[a])	
31			$Zn(OTf)_2$: 0.2 equiv.	58	42[a])	
32			$Zn(OTf)_2$: 0.3 equiv.	48	52[a])	
33			$Zn(OTf)_2$: 0.5 equiv.	37	63[a])	
34			$Zn(OTf)_2$: 0.7 equiv.	34	66[a])	
35			$Zn(OTf)_2$: 1.0 equiv.	20	80[a])	
36	**2** (CD_3CN/D_2O 2 : 1)	**A**: 2.0 equiv.	$Zn(OTf)_2$: 0.5 equiv.	93	7	0

[a]) Sum of mono- and bis-hemiacetals.

To determine the ideal stoichiometric relationship for hemiacetal formation, we varied the amount of cation added to the solution between 0 and 1 mol-equiv. Data obtained for the reaction between aldehydes **1** and **2** with geraniol (**B**) are collected in *Table 1* (*Entries 15–20* and *30–35*). As shown in [17], the optimum ligand/Zn^{2+} ratio

for monoaldehyde **1** is *ca.* 2 : 1 (which corresponds to 0.5 equiv. of $Zn(OTf)_2$). Addition of more Zn^{2+} to the solution reduced the amount of hemiacetal formed. The structures of zinc complexes **3**–**6** obtained by reaction of aldehyde **1** with fragrance alcohols **A**–**D** in the presence of $Zn(OTf)_2$ should thus correspond to those illustrated in *Fig. 2*. In the case of dicarbaldehyde **2**, the ^{1}H-NMR signals of the mono- and bis-hemiacetals could not be distinguished. Nevertheless, a constant increase of hemiacetal formation was observed with an increasing amount of Zn^{2+} salt added.

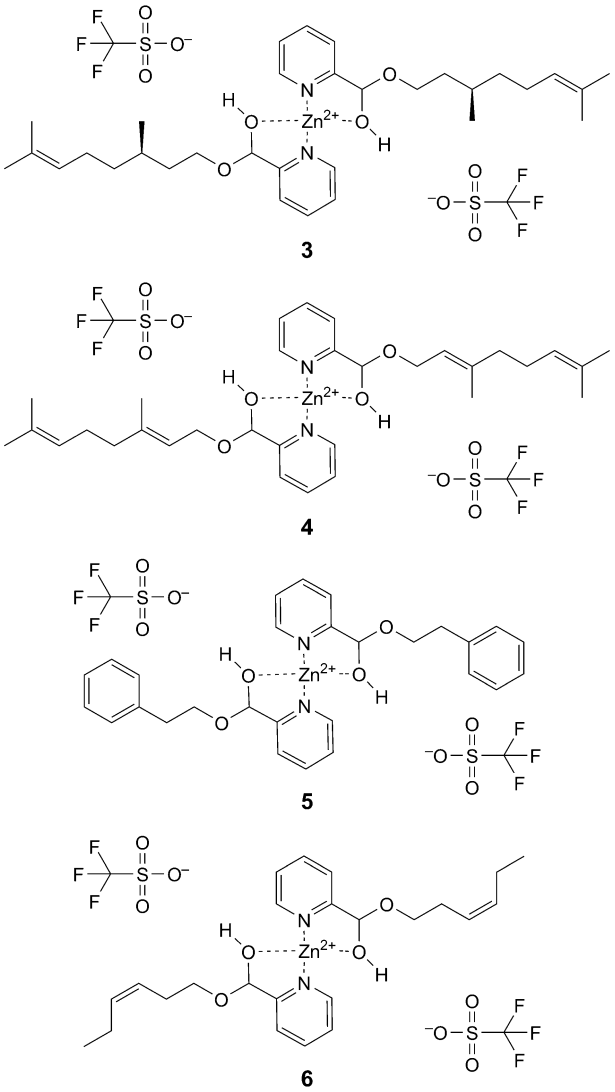

Fig. 2. *Proposed structures of hemiacetals* **3**–**6** *obtained by equilibration of* **1** *with fragrance aldehydes* **A** – **D**, *respectively, in the presence of* $Zn(OTf)_2$ *as the stabilizing salt*

The structures of the hemiacetal complexes **3**–**6** were analyzed by ^{1}H- and ^{13}C-NMR spectroscopy. *Fig. 3* shows the enlarged aromatic region of the 2D ^{1}H,^{13}C-HSQC spectrum of complex **3**. Two sets of data can be distinguished, notably the peaks of the unreacted aldehyde **1** and those corresponding to the hemiacetal formed by reaction of **1** with citronellol (**A**) in the Zn^{2+} complex. A striking feature of the ^{13}C-NMR signals of the hemiacetal complex is that a significant line broadening was observed for the *doublet*s of the C-atoms in *ortho*- and *para*-position to the N-atom (which almost disappeared in the baseline of the spectrum). Furthermore, a general broadening of the signals corresponding to the aromatic H-atoms of the pyridine moiety was noticed, while the signals of the free aldehyde remained narrow and well-resolved. This particular line-broadening pattern, which was attributed to the chemical exchange of the hemiacetal in the Zn^{2+} complex, turned out to be a general feature that was observed for all hemiacetal complexes studied in this work. The NMR spectra recorded for the same hemiacetals in the absence of Zn^{2+} did not reveal any line-broadening effects (data not shown). Therefore, the strong line broadening indicates the successful complexation of the hemiacetals to Zn^{2+} and thus confirms the structure assignment of complexes **3**–**6**.

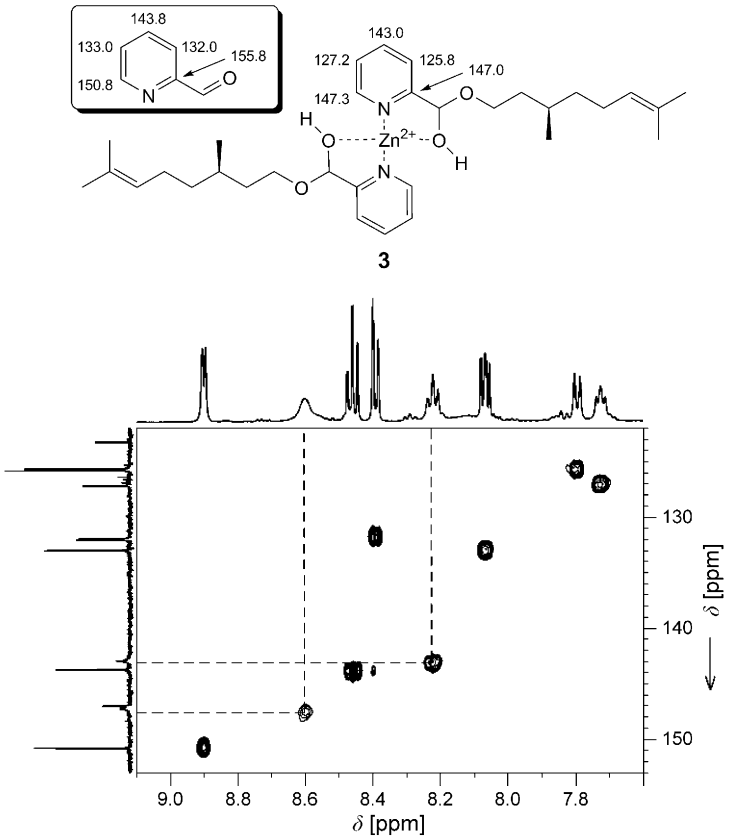

Fig. 3. *Enlarged aromatic region of the ^{1}H,^{13}C-HSQC spectrum of stabilized hemiacetal* **3** *together with unreacted aldehyde* **1** *and citronellol* (**A**)

The solubility of the stabilizing salt turned out to be one of the most important prerequisites for the successful generation of the hemiacetal complexes. Other organic solvents that allow dissolution of a series of metal salts are dimethyl sulfoxide (DMSO) or acetone. Acetone, in particular, is interesting, as this solvent is compatible with the targeted perfumery applications. While DMSO turned out to be unsuitable for the formation of the hemiacetal complexes, $Zn(OTf)_2$ was successfully dissolved in acetone (after sonication). *Table 1* (*Entries 21–24*) lists the amounts of free alcohol and stabilized hemiacetal complexes obtained from the reaction of aldehyde **1** with fragrance alcohols **A**–**D** in deuterated acetone. The yields of hemiacetals formed are slightly lower in acetone than in CD_3CN, but still in a range that should be interesting for practical application[2]). With $Cu(OTf)_2$ as the stabilizing salt, we obtained *ca*. 15% of hemiacetal in a mixture of aldehyde **1** and geraniol (**B**).

Because H_2O, as well as alcohols such as MeOH or EtOH, competes with the fragrance alcohols to hydrate aldehydes, a decrease of the amount of stabilized hemiacetals in favor of the hydrated aldehyde was expected in aqueous solution. To obtain information about the efficiency of hemiacetal formation in an aqueous environment, we performed measurements in CD_3CN/D_2O 2:1. For the analysis, the aldehyde and the fragrance alcohol were dissolved in CD_3CN, and the stabilizing $Zn(OTf)_2$ in D_2O. Pipetting equivalent amounts of each solution into an NMR tube resulted in the final mixture of CD_3CN/D_2O 2:1. As in previous experiments, the final aldehyde concentration was kept at 0.15 mol l^{-1}; 0.5 mol-equiv. of $Zn(OTf)_2$ were used with respect to the aldehyde concentration. The data in *Table 1* (*Entries 25*, *26*, and *36*) indicated that the formation of hemiacetals was reduced in the presence of H_2O. The percentages of hemiacetals varied between 3 and 5% in the case of aldehyde **1** (*Entries 25* and *26*), amounts comparable to those measured in the absence of the stabilizing cations (*Entries 1* and *2*). In the presence of H_2O, the amount of hemiacetal formed from dialdehyde **2** and citronellol (*Entry 36*) dropped to *ca.* 1/3 of that in the non-stabilized mixture studied previously (*Entries 27* and *28*).

With the formation of the hemiacetals proceeding quite rapidly [17], the presence of H_2O should hydrolyze the stabilized complexes instantaneously. As the next step, we investigated the release of the volatile fragrance alcohol from hemiacetal **5** under more realistic conditions, in particular in the presence of H_2O.

Release of Alcohols from Stabilized Hemiacetals in H_2O. H_2O is the most common solvent in perfumery, with many cleaning and conditioning agents being based on aqueous formulations. The performance of functional perfumery formulations, such as bodycare or household products, is often judged on the freshness and long-lasting character of the fragrance perception. The cleaning and softening of textiles represents a typical example of an application requiring an improved duration of fragrance release over several days. Fabric detergents are conceived to remove hydrophobic substances from the fabric surface or to prevent their deposition. It is, therefore, particularly challenging to deposit large amounts of fragrances during fabric cleaning. Therefore, fragrances are often deposited during the fabric conditioning (softening) step following the washing process.

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[2]) A weak competition of acetone in forming the stabilized hemiacetal complex cannot be ruled out. However, this possibility has not been examined in further detail within this work.

In the present work, we investigated the performance of the stabilized hemiacetals described earlier in improving the long-lasting property of fragrance perception in fabric cleaning and conditioning. The evaporation of the fragrances released from the stabilized hemiacetals on dry cotton was analyzed by dynamic headspace analysis [19] after the washing or conditioning process. Dynamic headspace analysis allows quantification of the amount of fragrance above the cotton surface without requiring complicated sample preparation. The desired increased duration of fragrance perception is achieved if the samples containing the stabilized hemiacetal give rise to higher headspace concentrations than that of a reference sample containing an equimolar amount of the corresponding unmodified fragrance alcohol.

Solid powder detergents are interesting supports for the stabilized hemiacetal complex, as the dry powder should allow storage of the complex without major decomposition due to hydrolysis. To simulate a powder-detergent washing process, we prepared solutions of stabilized hemiacetal complex **5** and a reference sample of unmodified 2-phenylethanol (**C**) in MeCN, and left them standing for 3 d. The solutions were then added to a commercially available non-perfumed powder detergent, which was then placed into two stainless steel containers. After addition of tap water, two cotton sheets were added to each of the containers and the containers rotated in a water bath to simulate a machine washing process. The cotton sheets were then rinsed by agitating them manually in cold tap water before line-drying them overnight. Two of the sheets (one with the hemiacetal complex and one without) were analyzed the next day.

The dry cotton sheets were then put into a dynamic headspace sampling cell (*ca.* 160 ml) and exposed to a constant airflow [20]. After equilibrating the system for a few minutes, the volatiles were adsorbed on a clean poly(2,6-diphenyl-*p*-phenylene oxide) (*Tenax*®) cartridge at constant time intervals. The cartridges were then thermally desorbed, and headspace concentrations (in ng l^{-1}) were obtained by external standard calibrations of the corresponding fragrance alcohol. The data in *Table 2* and *Fig. 4* illustrate that a slight long-lasting effect of fragrance release was achieved after 1 d.

At the beginning of the measurements (for *ca.* 150 min), the headspace concentrations increased before reaching a plateau or slightly decreasing again. This initial rise

Table 2. *Average Dynamic Headspace Concentrations and Standard Deviations* (in parentheses) *of 2-Phenylethanol* (**C**) *Measured on Dry Cotton after Washing with a Powder Detergent Containing the Hemiacetal Stabilized with* $Zn(OTf)_2$ (**5**) *or an Equimolar Amount of Unmodified 2-Phenylethanol* (reference)

Time [min]	1 day	1 day
	Reference [ng l^{-1}]	From hemiacetal stabilized with $Zn(OTf)_2$ (**5**) [ng l^{-1}]
45	0.8 (± 0.5)	0.9 (± 0.3)
105	1.1 (± 1.0)	1.4 (± 0.8)
165	1.2 (± 1.1)	1.5 (± 0.8)
225	1.0 (± 0.7)	1.5 (± 0.7)
285	0.9 (± 0.6)	1.6 (± 0.6)
345	0.9 (± 0.6)	1.6 (± 0.5)
405	0.8 (± 0.5)	1.7 (± 0.4)
465	0.8 (± 0.5)	1.8 (± 0.4)

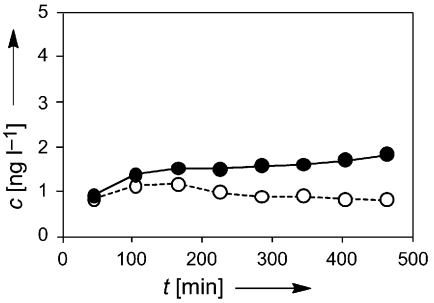

Fig. 4. *Comparison of the headspace concentrations of 2-phenylethanol released from stabilized hemiacetal complex* **5** (—●—) *and free 2-phenylethanol* (—○—) *measured in a powder detergent application on dry cotton after drying for 1 day*

was generally observed for this type of measurement and attributed to the conditioning of the line-dried cotton sheet in the headspace sampling cell [20]. Furthermore, because the headspace measurements were carried out under realistic everyday conditions, the measured concentrations showed large variations, probably due to the lack of control of various parameters (such as temperature, humidity, and convection) during the line drying of the cotton sheets. Nevertheless, relative values obtained by comparison to the respective reference samples were found to be quite reproducible.

In an additional experiment, we analyzed the performance of the stabilized hemiacetal with respect to a reference sample in a surfactant-based aqueous formulation such as a fabric softener. Cationic surfactants, such as quaternized triethanolamine esters of fatty acids (TEA-esterquats) [21], have fabric-softening properties and are efficiently deposited onto cotton from aqueous media. Fragrances, as well as fragrance precursors, are expected to be incorporated into the surfactant structure and, thus, to be carried to the cotton surface [22].

For the measurements, a solution of hemiacetal **5** (stabilized with $Zn(OTf)_2$) was prepared in MeCN and left standing for 3 d before being added to a TEA-esterquat formulation. The mixture was then diluted with demineralized H_2O, and a cotton sheet was added, which was manually stirred for 3 min and left standing for 2 min. The sheet was then wrung out and line-dried overnight. Another cotton sheet prepared in the same way was left drying for 3 d. The dry cotton sheets were then put into a dynamic headspace sampling cell as described in [20]. After equilibrating, the volatiles were adsorbed on a clean *Tenax*® cartridge at constant time intervals. The cartridges were then desorbed, and headspace concentrations were obtained by external standard calibrations. Reference samples containing equimolar amounts of 2-phenylethanol were prepared and analyzed in the same way. The data are summarized in *Table 3* and illustrated in *Fig. 5*.

After drying for 1 d, almost identical headspace concentrations were measured for the free fragrance alcohol and the alcohol released from stabilized hemiacetal **5** (*Fig. 5*). This indicated that, indeed, the complex rapidly exchanged the fragrance alcohol against H_2O to give free 2-phenylethanol, which then evaporated from the cotton surface. The fact that the headspace concentrations of 2-phenylethanol released from **5** slightly increased from *ca.* 95 ng l^{-1} after 1 d (*Fig. 5*,*a*, solid line) to *ca.* 110 ng l^{-1} after 3 d (*Fig. 5*,*b*, solid line), while those of the corresponding free alcohol in the reference sample decreased from *ca.* 95 ng l^{-1} after 1 d (*Fig. 5*,*a*, dotted line) to *ca.*

Table 3. *Average Dynamic Headspace Concentrations and Standard Deviations* (in parentheses) *of 2-Phenylethanol* (**C**) *Measured on Dry Cotton after Washing with a Cationic Surfactant Formulation Containing the Hemiacetal Stabilized with $Zn(OTf)_2$* (**5**) *or an Equimolar Amount of Unmodified 2-Phenylethanol* (reference)

Time [min]	1 day		3 days	
	Reference [ng l^{-1}]	From hemiacetal stabilized with $Zn(OTf)_2$ (**5**) [ng l^{-1}]	Reference [ng l^{-1}]	From hemiacetal stabilized with $Zn(OTf)_2$ (**5**) [ng l^{-1}]
30	14.4 (± 9.0)	11.5 (± 0.2)	12.4 (± 13.8)	15.5 (± 12.7)
90	33.9 (± 7.7)	44.8 (± 25.3)	19.8 (± 18.0)	44.4 (± 13.7)
150	61.0 (± 27.0)	78.1 (± 24.3)	33.0 (± 32.1)	86.9 (± 7.1)
210	76.1 (± 38.8)	87.4 (± 26.9)	62.4 (± 35.6)	104.7 (± 14.6)
270	90.9 (± 32.2)	94.0 (± 28.8)	70.8 (± 25.7)	108.8 (± 9.1)
330	92.8 (± 38.3)	95.5 (± 33.2)	70.7 (± 21.5)	109.2 (± 13.0)
390	95.6 (± 41.1)	96.7 (± 31.7)	77.8 (± 16.1)	112.3 (± 14.2)
450	94.6 (± 42.1)	96.3 (± 34.7)	77.4 (± 11.4)	112.1 (± 15.0)

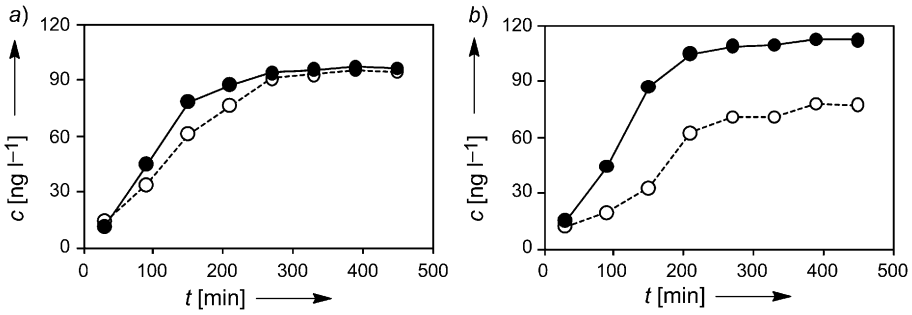

Fig. 5. *Comparison of the headspace concentrations of 2-phenylethanol released from stabilized hemiacetal complex* **5** (—●—) *and free 2-phenylethanol* (—○—) *measured in a fabric softener application on dry cotton after drying for 1 day* (*a*) *and 3 days* (*b*)

75 ng l^{-1} after 3 d (*Fig. 5*, *b*, dotted line), demonstrated the desired slow release effect of the stabilized hemiacetal with respect to the reference despite the expected rapid hydrolysis in the presence of H_2O (see also *Table 3*).

Conclusions. – Hemiacetals of pyridine-2-carbaldehyde derivatives and a series of volatile alcohols can be stabilized in organic solution in the presence of protons or different metal cations such as Zn^{2+}. In MeCN, up to 50% of stabilized hemiacetals were formed in solution. Acetone can be used as an alternative solvent to prepare the hemiacetal complexes. $Zn(OTf)_2$ was found to be a versatile stabilizing salt, being quite soluble in a series of organic solvents.

The performance of the stabilized hemiacetals as delivery systems for the controlled release of volatile fragrance alcohols was investigated in fabric cleaning and conditioning applications. Dynamic headspace analysis on dry cotton showed that a slight long-lasting effect of fragrance release was achieved from a powder detergent

washing process after 1 d. Despite the presence of H_2O in the surfactant formulation, an even more pronounced slow-release effect was achieved in a fabric conditioning process after 3 d.

Besides applications in functional perfumery, stabilized hemiacetals might also find use in the screening of pharmaceutically active compounds and receptors. Nevertheless, on the basis of the current data, it is probably too early to evaluate the full potential of stabilized hemiacetals as delivery systems for the controlled release of bioactive compounds.

Experimental Part

General. Commercially available reagents and solvents were used without further purification. Demineralized H_2O was obtained from a *Millipore Synergy 185* H_2O purifier. ^{1}H- and ^{13}C-NMR spectra were recorded at 25° on a *Bruker* 400 MHz *DPX* spectrometer, δ [ppm] downfield from Me_4Si as internal standard, J in Hz. Standard pulse sequences and parameters were used for one-dimensional ^{1}H- and ^{13}C-NMR spectra and for 2D, gradient-selected COSY, NOESY, ^{1}H-,^{13}C-HSQC, and ^{1}H-,^{13}C-HMBC spectra.

NMR Analysis. In a typical experiment, 0.9 mmol of the aldehyde, 1 mol-equiv. of fragrance alcohol, and 0.5 mol-equiv. of stabilizing salt were weighed into 2 ml of MeCN. Then, 0.3 ml of each soln. were pipetted into an NMR tube and left standing overnight. ^{1}H-NMR Spectra were recorded with 320 scans, and the amount of hemiacetal was determined by integrating the signals of the H-atoms at the C-atom adjacent to the O-atom of the alcohol moiety for both the hemiacetal and the free alcohol in the compound mixture. The following signals of the CH_2OH and CH_2OR groups (in CD_3CN and in the presence of $Zn(SO_3CF_3)_2$) of the different alcohols and their respective hemiacetals were considered for the quantification of the compounds in different mixtures: *citronellol* (**A**) 3.5 (*m*) and 3.7 (*m*) ppm; *geraniol* (**B**) 4.0 (*d*, CHOH) and 4.2 (*d*, CHOR) ppm; *2-phenylethanol* (**C**) 3.7 (*t*) and 3.9 (*m*) ppm; *hex-3-en-1-ol* (**D**) 3.5 (*t*) and 3.7 (*m*) ppm. The formation of hemiacetal complexes **3**–**6** in CD_3CN was also verified by ^{13}C-NMR spectroscopy (2000 scans).

Complex **3**: $Zn(OTf)_2$ (0.5 equiv.), **1** (1 equiv.), and **A** (1 equiv.). ^{1}H-NMR (400 MHz, CD_3CN): 8.60 (br. *s*, 1 H); 8.22 (*t*, J = 7.6, 1 H); 7.80 (*d*, J = 8.1, 1 H); 7.73 (*d*, J = 6.3, 1 H); 5.99 (*s*, 1 H); 5.11 (*m*, 1 H); 3.72 (*m*, 2 H); 1.97 (*m*, 2 H); 1.65 (*s*, 3 H); 1.63 (*m*, 1 H); 1.58 (*s*, 3 H); 1.52 (*m*, 1 H); 1.43–1.10 (*m*, 3 H); 0.87 (*d*, J = 6.7, 3 H). ^{13}C-NMR (100.6 MHz, CD_3CN): 147.3 (br. *d*); 147.0 (*s*); 143.0 (br. *d*); 131.9 (*s*); 127.2 (*d*); 125.8 (*d*); 125.7 (*d*); 121.6 (*s*, ^1J (^{13}C,^{19}F) = 320); 93.6 (*d*); 93.5 (*d*); 67.8 (*t*); 67.7 (*t*); 37.8 (*t*); 37.7 (*t*); 37.1 (*t*); 37.0 (*t*); 30.3 (*d*); 30.1 (*d*); 26.1 (*t*); 25.9 (*q*); 19.7 (*q*); 17.7 (*q*).

Complex **4**: $Zn(OTf)_2$ (0.5 equiv.), **1** (1 equiv.), and **B** (1 equiv.). ^{1}H-NMR (400 MHz, CD_3CN): 8.60 (br. *s*, 1 H); 8.23 (*t*, J = 7.6, 1 H); 7.78 (*d*, J = 7.9, 1 H); 7.27 (*t*, J = 6.3, 1 H); 6.00 (*s*, 1 H); 5.34 (*t*, J = 6.6, 1 H); 5.11 (*m*, 1 H); 4.23 (*d*, J = 6.9, 2 H); 2.09 (*m*, 2 H); 2.00 (*m*, 2 H); 1.65 (*s*, 3 H); 1.64 (*s*, 3 H); 1.59 (*s*, 3 H). ^{13}C-NMR (100.6 MHz, CD_3CN): 147.3 (br. *d*); 147.3 (*s*); 143.1 (br. *d*); 138.9 (*s*); 132.7 (*s*); 127.1 (*d*); 125.7 (*d*); 124.9 (*d*); 121.7 (*s*, ^1J (^{13}C,^{19}F) = 320); 120.4 (*d*); 92.8 (*d*); 65.7 (*t*); 40.2 (*t*); 27.1 (*t*); 25.9 (*q*); 17.8 (*q*); 16.7 (*q*).

Complex **5**: $Zn(OTf)_2$ (0.5 equiv.), **1** (1 equiv.), and **C** (1 equiv.). ^{1}H-NMR (400 MHz, CD_3CN): 8.57 (br. *s*, 1 H); 8.20 (*m*, 1 H); 7.72 (*t*, J = 6.1, 1 H); 7.64 (*d*, J = 7.3, 1 H); 7.28 (*m*, 2 H); 7.24–7.19 (*m*, 3 H); 5.98 (*s*, 1 H); 3.90 (*m*, 2 H); 2.91 (*t*, J = 6.8, 2 H). ^{13}C-NMR (100.6 MHz, CD_3CN): 147.2 (*s*); 147.0 (br. *d*); 143.3 (br. *d*); 139.7 (*s*); 130.0 (*d*); 129.4 (*d*); 127.4 (*d*); 127.3 (*d*); 125.7 (*d*); 121.7 (*s*, ^1J (^{13}C,^{19}F) = 320); 93.5 (*d*); 70.0 (*t*); 36.5 (*t*).

Complex **6**: $Zn(OTf)_2$ (0.5 equiv.), **1** (1 equiv.), and **D** (1 equiv.). ^{1}H-NMR (400 MHz, CD_3CN): 8.61 (br. *s*, 1 H); 8.25 (*m*, 1 H); 7.83 (*d*, J = 7.8, 1 H); 7.75 (*t*, J = 6.1, 1 H); 6.00 (*s*, 1 H); 5.47 (*m*, 1 H); 5.33 (*m*, 1 H); 3.69 (*m*, 2 H); 2.35 (*td*, J = 6.8, 6.8, 2 H); 2.04 (*qd*, J = 7.5, 7.5, 2 H); 0.94 (*t*, J = 7.5, 3 H). ^{13}C-NMR (100.6 MHz, CD_3CN): 147.2 (*s*); 147.2 (br. *d*); 143.0 (br. *d*); 134.9 (*d*); 127.3 (*d*); 125.8 (*d*); 125.7 (*d*); 121.7 (*s*, ^1J (^{13}C,^{19}F) = 320); 93.5 (*d*); 69.2 (*t*); 28.2 (*t*); 21.3 (*t*); 14.6 (*q*).

Dynamic Headspace Analysis on Cotton (from a Powder Detergent). Stabilized hemiacetal **5** was prepared by mixing 1.2 ml of a soln. containing 96.3 mg of **1** in 2 ml of MeCN, 1.2 ml of a soln. containing

109.8 mg of **C** in 2 ml of MeCN, and 164.0 mg of $Zn(OTf)_2$ as the stabilizing salt in 2 ml of MeCN. Similarly, a reference sample was prepared by adding 2.4 ml of MeCN to 1.2 ml of the soln. of **C**. The solns. were left standing at r.t. for 3 d.

Then, 1.8 g of a non-perfumed, commercially available powder detergent (*Via Professional Sensitive* from *Unilever*), 2 ml of the stabilized hemiacetal soln., 400 ml of tap water, and two cotton sheets (*EMPA* cotton test cloth Nr. 221; pre-washed with an unperfumed detergent powder and cut to *ca.* 12 × 12 cm) were added to a stainless steel container of a *Linitest*® washing-machine simulator (*Heraeus*). This procedure was repeated with a second container, with the corresponding reference sample replacing the hemiacetal soln. The containers were fixed inside the machine and rotated at 45 °C for 20 min. The cotton sheets were rinsed by agitating them manually in 600 ml of tap water for 2 min and line-dried overnight. Two of the sheets (one with the hemiacetal complex and one without) were analyzed the next day. For the analysis, the sheets were each put into a headspace sampling cell (160 ml) thermostatted at 25°, and exposed to a constant airflow of 200 ml min^{-1}. The air was filtered through active charcoal and aspirated through a sat. soln. of NaCl (to ensure a constant humidity of the air of *ca.* 75%). After equilibrating for 15 min, the volatiles were adsorbed during 30 min on a clean *Tenax*® cartridge and 30 min on a waste cartridge, which was discarded after the measurements. The sampling was repeated seven times every hour. The cartridges were thermally desorbed on a *Perkin-Elmer TurboMatrix 350* desorber coupled to a *Perkin-Elmer AutoSystem XL* gas chromatograph equipped with a *J&W Scientific DB1* cap. column (30 m, i.d. 0.45 mm, film 0.42 μm) and a *Perkin-Elmer TurboMass Upgrade* MS detector. The volatiles were analyzed in the single-ion monitoring (SIM) mode using a two-step temp. gradient starting from 60° to 110° at 2° min^{-1} and then going to 260° at 45° min^{-1}. Headspace concentrations (in ng l^{-1}) were obtained by external standard calibration of the corresponding fragrance alcohol using EtOH solns. of five different concentrations. Each calibration soln. (0.1 μl) was injected onto *Tenax*® cartridges, which were immediately desorbed under the same conditions as those resulting from the headspace sampling. Average values were obtained from three measurements.

Dynamic Headspace Analysis on Cotton (from a Fabric Softener). Stabilized hemiacetal **5** was prepared by mixing 0.6 ml of a soln. containing 96.5 mg of pyridine-2-carbaldehyde (**1**) in 2 ml of MeCN, 0.6 ml of a soln. containing 109.7 mg of **C** in 2 ml of MeCN, and 0.6 ml of a soln. containing 164.0 mg of $Zn(OTf)_2$ as the stabilizing salt in 2 ml of MeCN. Similarly, a reference sample was prepared by adding 1.2 ml of MeCN to 0.6 ml of the soln. of **C**. The solutions were left standing at r.t. for 3 d.

Four beakers, each containing 1.8 g of a fabric softener formulation consisting of *Stepantex*® *VL 90 A* (16.5% (*w*/*w*)), $CaCl_2$ (10% aq. soln., 0.6% (*w*/*w*)), and demineralized H_2O (82.9% (*w*/*w*)) were prepared. Then, 1 ml of the stabilized hemiacetal soln. was pipetted into each of the first two beakers and 1 ml of the reference soln. of **C** into each of the two other beakers. Then, 600 ml of tap water and one cotton sheet were added to each beaker. The sheets were agitated manually for 3 min, left standing for 2 min, wrung out by hand, weighed to obtain a constant quantity of residual H_2O, and line-dried overnight. Two of the sheets (one with the hemiacetal and one without) were analyzed the next day, the other two after 3 d. For the analysis, the sheets were each put into a headspace sampling cell and analyzed as described in [20]. Headspace concentrations (in ng l^{-1}) were obtained by external standard calibration as described earlier. Average values were obtained from two measurements.

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