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Water triggered release of fragrances**

Journal:	<i>ChemComm</i>
Manuscript ID:	CC-COM-01-2015-000099.R1
Article Type:	Communication
Date Submitted by the Author:	04-Feb-2015
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COMMUNICATION

Pro-fragrant ionic liquids with stable hemiacetal motifs: Water triggered release of fragrances

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,

Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Stable liquid and solid salts in the form of elusive hemiacetals, appended with fragrant alcohols, have been synthesised as pro-fragrances, and the controlled release of these fragrances, triggered by water, is demonstrated.

Natural and synthetic perfume raw materials (PRMs) contain a multitude of chemical functional groups such as alcohols, aldehydes, ketones, esters, lactones, ethers, and nitriles.¹ Encapsulation of active compounds into suitable material matrices, or specifically designed polymer capsules, is the most widely used technique to prolong the longevity of a fragrance.² Fragrance- and flavour-containing oil-in-water (o/w) emulsions^{2c} are used in numerous applications, including personal care products, to control rate of release of these materials in order to enhance the quality of the product. Fragrances encapsulated in polymeric micro-capsules, that are susceptible to disintegrate slowly in contact with water, are also widely used in laundry applications where the compatibility of the polymer material with the fabric is thought to play a key role.³ From a supramolecular point of view, bio-compatible molecular container molecules such as cyclodextrins,⁴ and some of their derivatives have also been utilised in slow or controlled delivery of materials such as fragrances or drugs, through their weakly formed inclusion complexes.⁵ These inclusion complexes would set up an equilibrium between the entrapped guest molecules (fragrance or drug) in the host, and the released form, where that release can be designed to occur in a controlled fashion.

The final category of materials that are used for controlled delivery of substances are known as pro-substances (*i.e.* pro-drugs or pro-fragrances), where the substance is covalently bound to a matrix with a trigger mechanism initiated by a pH change,⁶ action of an enzyme targeting a covalent bond,⁷ photo-cleavage by light of a suitable wavelength,⁸ or thermal dissociation of the pro-substance.⁹ For PRM alcohols, pro-fragrances in the form of predesigned esters, where the release of the fragrance may be effected by a lipase enzyme,¹⁰ or changing to a higher pH of the medium.⁶ Furthermore, acetals and ketals have been used as pro-fragrances of alcohols; at more acidic

pH, the fragrance would be released.¹¹ Orthoesters and orthocarbonates derived from fragrant alcohols have also been used with acid mediated release.¹²

In this communication, the synthesis of rare linear hemiacetals³³ of fragrant alcohols³⁴ is described, as part of a reactive class of ionic liquids.³⁵ These pro-fragrant materials were synthesised with a labile reaction centre intentionally incorporated. The hemiacetal is attached to a non-volatile ionic matrix, to form a new class of pro-fragrances, where the release trigger is neutral water (see Figure 1), and the fragrance molecule is released cleanly and near quantitatively. To our knowledge, hemiacetal motifs have not previously been explored for delivery of materials such as fragrances, drugs or sensors. However, Davis *et al.* have demonstrated a related class of interesting materials,¹⁶ where a reactive ionic liquid system participates in a multicomponent equilibrium with alcohols and amines.

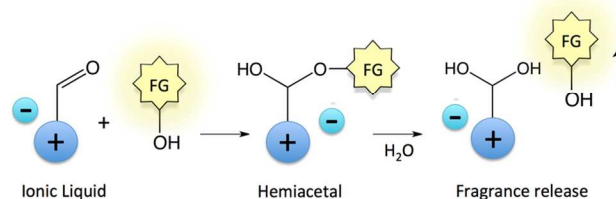
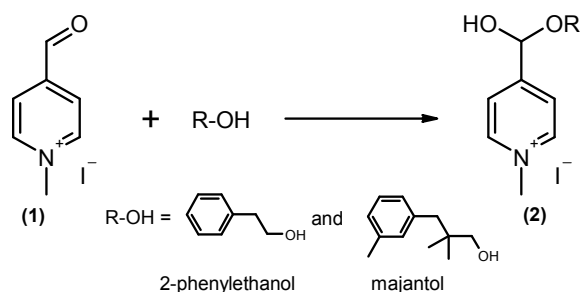


Figure 1: An illustration of the release of volatile alcohol perfumes from a non-volatile hemiacetal ionic liquid matrix, triggered by neutral water

When 1-methyl-4-formylpyridinium iodide was treated with a four-fold excess of fragrant alcohols without any solvent (see Scheme 1), the corresponding hemiacetals were isolated cleanly after removing the excess alcohols by treating the reaction mixture with dry diethyl ether, from which excess fragrant alcohol can be recovered.



Scheme 1: Reaction scheme for the synthesis of ionic liquids from fragrance alcohols

As shown in the scheme, two known alcohols, viz. 2-phenylethanol (R = PhCH₂CH₂) and majantol (R = 3-MeC₆H₄CH₂CMe₂CH₂), were used in this study. Compound (**2a**) was isolated as a crystalline solid (m.p. 105 °C) and (**2b**) as a liquid (T_g of 37 °C).

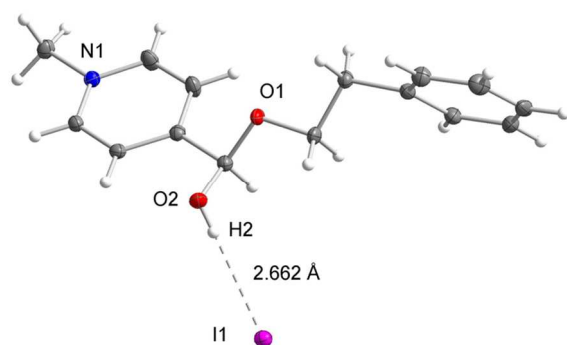


Figure 2: Partial X-ray crystal structure of the stable hemiacetal, (**2a**)

Single crystals of (**2a**), suitable for X-ray crystallography, were obtained from a CH₃CN-Et₂O mixture. The X-ray crystal structure of (**2a**) is shown in Figure 2. The clear presence of a hydrogen bond between –OH and the iodide anion with an O–H[⋯]I distance of 2.662(1) Å is observed, clearly stabilising the hemiacetal.

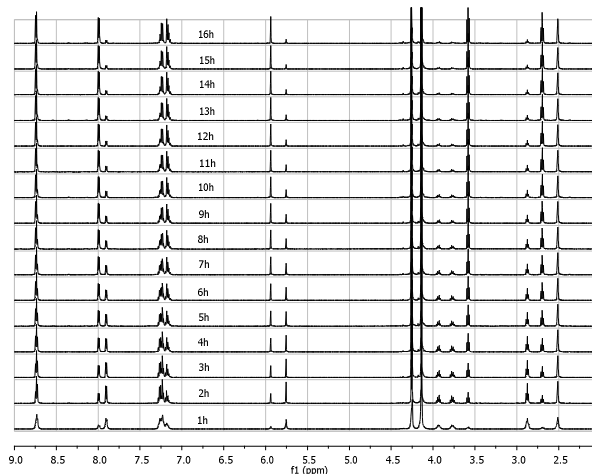


Figure 3: A stack plot of ¹H NMR spectra taken at varying times, at 30 °C, monitoring the reaction (at times from 1–16 h) between (**2a**) and water; concentration of (**2a**) is 15 mM in dms_o-d₆/D₂O (72:28; v/v).

The interaction between (**2a**) and water was monitored by ¹H NMR spectroscopy: a stack plot is shown in Figure 3 for the case where 28 % water (v/v) was added to a dms_o-d₆ solution. A kinetic run was performed to monitor the release of 2-phenylethanol. It was clearly shown that the release of the fragrant alcohol, triggered by neutral water, is clean and nearly quantitative. The two singlets seen between δ 6.0 and 5.5 belong to the acetal CH groups. The effect of water concentration upon the kinetics of fragrance release was then investigated. A set of data was obtained for the reaction profile for the release of 2-phenylethanol from (**2a**) in the presence of varying amounts of water; viz at 28 %, 38 %, 44 % and 50 % in dms_o-d₆ (see Figure 4). As expected, the rate of release of the fragrant alcohol, 2-phenylethanol, increased with the amount of water present in the solvent mixture.

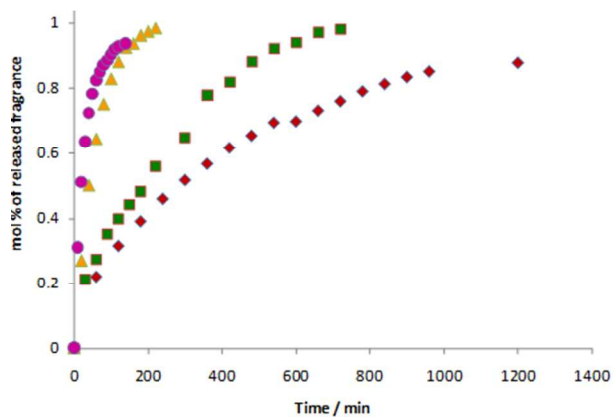


Figure 4: A kinetic reaction profile, at 30 °C, for releasing 2-phenylethanol from (**2a**) in dms_o-d₆ with 28 % (red diamonds), 38 % (green squares), 44 % (orange triangles) and 50 % (magenta circles) of added D₂O. The concentration of (**2a**) is 15 mM in all cases.

Similar results were obtained for pro-fragrance (**2b**) where the release of majantol is shown to be nearly quantitative (Figure 5).

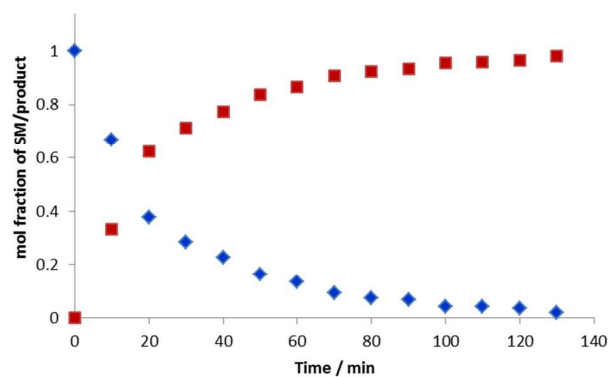


Figure 5: A kinetic reaction profile, at 30 °C, for releasing majantol from (**2b**) in CD₃CN-D₂O(60:40 v/v); mole fraction of (**2b**) vs time (blue diamonds); mole fraction of majantol vs time (red squares). The concentration of (**2b**) is 15 mM in all cases.

It is noteworthy that, in contrast to many known pro-fragrances with diverse release mechanisms,^{10a,17} the loss of fragrance material here

due to side reactions is minimal. In particular, in cases where enzymes were used as the trigger, up to 50 % of the active ingredient may be lost due to breakdown processes.

In conclusion, a new pro-fragrant motif that responds to neutral water as a release trigger for the fragrance is introduced here, demonstrating that control of release is dependent on the amount of water available. In addition, as these materials are also capable of responding to atmospheric humidity, they could display a form of 'sensor activity'. They may also respond to perspiration in personal care products.

We thank Dr. Marijana Blesic for valuable discussions, and Angela Brownlie and Lynsey Finlay for instrumental assistance. The NCS Southampton is acknowledged for crystal data collection.¹⁸

Notes and references

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† Electronic Supplementary Information (ESI) available: additional DSC, NMR, MS, crystal data and synthetic procedures are included here. See DOI: 10.1039/b000000x/

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