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Pro-fragrant ionic liquids with stable hemiacetal motifs: water-triggered release of fragrances†‡

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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 hemiacetals[13] of fragrant alcohols[14] is described, as part of a reactive class of ionic liquids.[15] 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 Fig. 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.

When 1-methyl-4-formylpyridinium iodide was treated with a four-fold excess of fragrant alcohols without any solvent (see Scheme 1), the corresponding hemi-acetals 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.

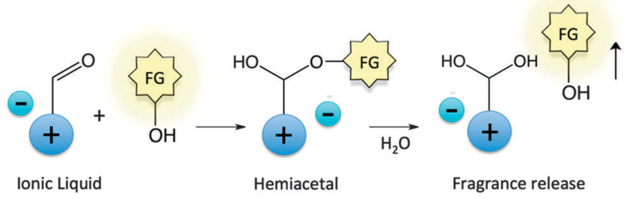

Fig. 1 An illustration of the release of volatile alcohol perfumes from a non-volatile hemiacetal ionic liquid matrix, triggered by neutral water.

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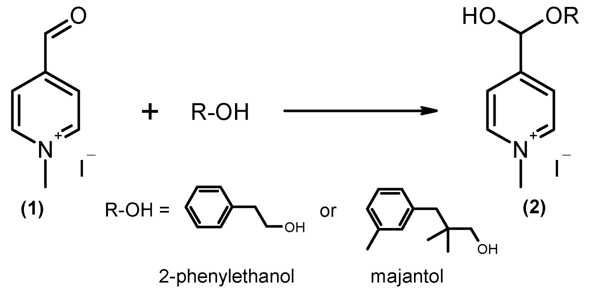
‡ Electronic supplementary information (ESI) available: Additional DSC, NMR, MS, crystal data and synthetic procedures are included here. CCDC 1042672. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc00099h



Scheme 1 Reaction scheme for the synthesis of ionic liquids from fragrance alcohols. (**2a**) and (**2b**) are derived from 2-phenylethanol and majantol, respectively.

As shown in the scheme, two known alcohols, *viz.* 2-phenylethanol (R = $PhCH_2CH_2$) and majantol (R = $3\text{-}MeC_6H_4CH_2\text{-}CMe_2CH_2$), 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).

Single crystals of (**2a**), suitable for X-ray crystallography, were obtained from a $CH_3CN\text{–}Et_2O$ mixture. The X-ray crystal structure of (**2a**) is shown in Fig. 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.

The interaction between (**2a**) and water was monitored by ^1H NMR spectroscopy: a stack plot is shown in Fig. 3 for the case where 28% water (v/v) was added to a DMSO-d_6 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 DMSO-d_6 (see Fig. 4). As expected, the rate of release of the fragrant alcohol, 2-phenylethanol, increased with the amount of water present in the solvent mixture.

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

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

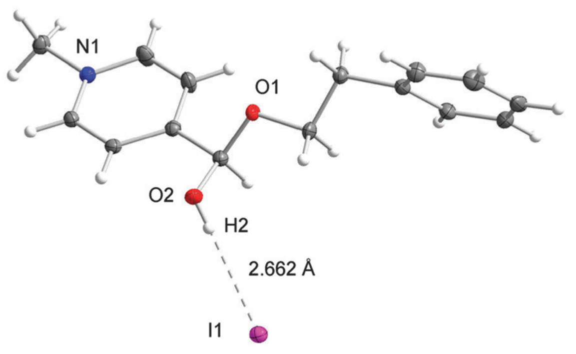


Fig. 2 Partial X-ray crystal structure of the stable hemi-acetal, (**2a**).

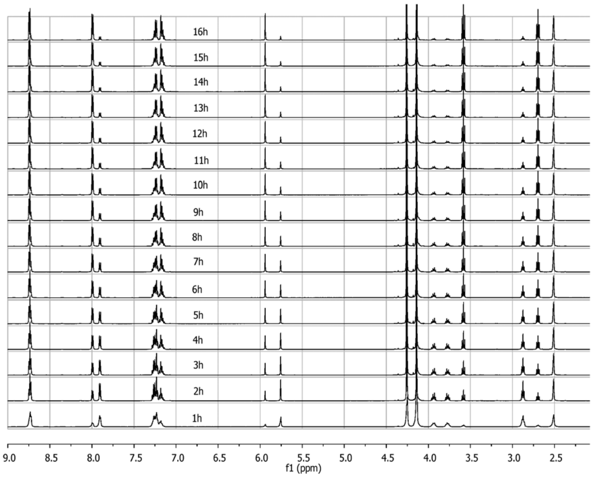


Fig. 3 A stack plot of ^1H (400 MHz) NMR spectra taken at varying times, at 30 °C, monitoring the reaction (at times from 1–16 h) between (**2a**) and water; concentration of (**2a**) is 15 mM in DMSO-d_6/D_2O (72 : 28; v/v).

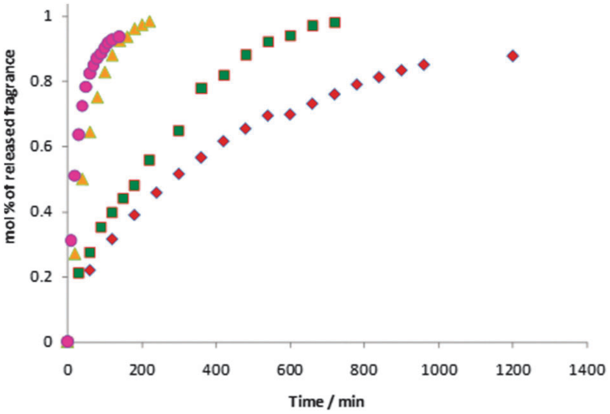


Fig. 4 A kinetic reaction profile, at 30 °C, for releasing 2-phenylethanol from (**2a**) in DMSO-d_6 with 28% (red diamonds), 38% (green squares), 44% (orange triangles) and 50% (magenta circles) of added D_2O. The concentration of (**2a**) is 15 mM in all cases.

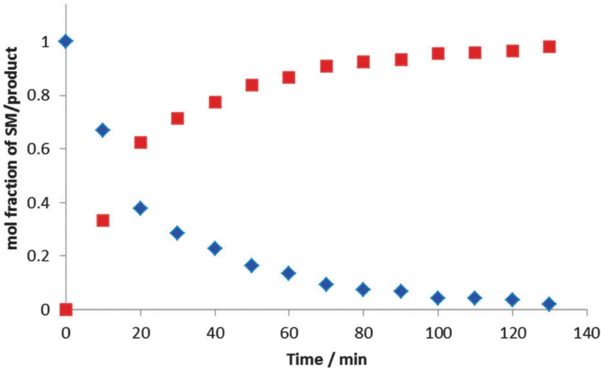


Fig. 5 A kinetic reaction profile, at 30 °C, for releasing majantol from (**2b**) in $CD_3CN\text{–}D_2O$(60 : 40 v/v); mole fraction of (**2b**) *vs.* time (blue diamonds); mole fraction of majantol *vs.* time (red squares). The concentration of (**2b**) is 15 mM in all cases.

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.

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Notes and references

1 *Chemistry and Technology of Flavors and Fragrances*, ed. D. J. Rowe, Blackwell, Oxford, 2005; *The Chemistry of Fragrances*, ed. D. Phybus and C. Sell, The Royal Society of Chemistry, Cambridge, 1999; P. J. Teisseire, *Chemistry of Fragrant Substances*, VCH, Weinheim, 1994; *Perfumes: Art, Science and Technology*, ed. P. M. Muller and D. Lamparsky, Elsevier Applied Science, 1994; H. Surburg and J. Panten, *Common Fragrance and Flavor Materials*, Wiley-VCH, Weinheim, 5th edn, 2006; H. Surburg and J. Panten, *Common Fragrance and Flavour Materials*, Wiley-VCH, Wienheim, 5th edn, 2006.

2 (*a*) Z. Xiao, T. Tian, J. Hu, M. Wang and R. Zhou, *Flavour Fragrance J.*, 2014, **29**, 22–34; (*b*) C. Yuan, Z. Lu and Z. Jin, *Food Chem.*, 2014, **152**, 140–145; (*c*) A. V. Sadovoy, M. V. Lomova, M. N. Antipina, N. A. Braun, G. B. Sukhorukov and M. V. Kiryukhin, *ACS Appl. Mater. Interfaces*, 2013, **5**, 8948–8954.

3 C. P. Chang and T. Dobashi, *Colloids Surf., B*, 2003, **32**, 257–262; S. Leclercq, K. Harlander and G. A. Reineccius, *Flavour Fragrance J.*, 2009, **24**, 17–24; P. Lertsutthiwong, P. Rojsitthisak and U. Nimmannit, *Mater. Sci. Eng., C*, 2009, **29**, 856–860.

4 F. Stoddart, *Cyclodextrins*, Royal Society of Chemistry, Cambridge, 1989; D. J. Cram and J. M. Cram, in *Container Molecules and their Guests, Monographs in Supramolecular chemistry*, ed. J. F. Stoddart, 1994.

5 U. Numanoğlu, T. Şen, N. Tarimci, M. Kartal, O. M. Y. Koo and H. Önyüksel, *AAPS PharmSciTech*, 2007, **8**, E1–E9; W. C. E. Schofield and J. P. S. Badyal, *ACS Appl. Mater. Interfaces*, 2011, **3**, 2051–2056; S. D. Rodrıguez and D. L. Bernik, *Appl. Spectrosc.*, 2013, **67**, 884–891; C. Yuan, Z. Lu and Z. Jin, *Food Chem.*, 2014, **152**, 140–145.

6 J.-Y. Saint Laumer, E. Frerot and A. Herrmann, *Helv. Chim. Acta*, 2003, **86**, 2871; A. D. Headley, S. D. Starnes, L. Y. Wilson and G. R. Famini, *J. Org. Chem.*, 1994, **59**, 8040–8046; S. Espinosa, E. Bosch and M. Rosus, *Anal. Chem.*, 2002, **74**, 3809–3818; J. M. Gardlik and M. R. Sivik, WO 98/07405, 1998; D. Anderson and G. Frater, EP 0911315, 1999.

7 F. Flachsmann, M. Gautschi, J.-P. Bachmann and G. Brunner, *Chem. Biodiversity*, 2008, **5**, 1115–1136; D. Anderson and G. Frater, *Givaudan Roure SA*, EP 0936211, 1999; S. B. Lyon *et al.*, U. S. Pat., 9111988, 1991; P. Kraft, *Chimia*, 2001, **55**, 379–387.

8 S. Rochat, C. Minardi, J.-Y. Saint Laumer and A. Herrmann, *Helv. Chim. Acta*, 2000, **83**, 1645–1671; V. N. R. Pillai, *Synthesis*, 1980, 1–26; C. G. Bochet, *J. Chem. Soc., Perkin Trans. 1*, 2002, 125–142; A. P. Pelliccioli and J. Wirz, *Photochem. Photobiol. Sci.*, 2002, **1**, 441–458; V. Lemieux, S. Gauthier and N. R. Branda, *Angew. Chem., Int. Ed.*, 2006, **45**, 6820–6824; J. Lage Robles and C. G. Bochet, *Org. Lett.*, 2005, **7**, 3545–3547.

9 Z. Xiao, T. Tian, J. Hu, M. Wang and R. Zhou, *Flavour Fragrance J.*, 2014, **29**, 22–34; W.-C. Hsieha, C.-P. Chang and Y. L. Gao, *Colloids Surf., B*, 2006, **53**, 209–214; R. D. Rogers, D. T. Daly, G. Gurau, D. MacFarlane, J. Turanjanin, P. M. Dean, J. L. Scott, K. Bica and K. R. Seddon, WO 2010/078300A1, 2010.

10 (*a*) M. Blesic, H. Q. N. Gunaratne, P. Nockemann, P. McCarron and K. R. Seddon, *RSC Adv.*, 2013, **3**, 329–333; (*b*) V. Athawale, N. Manjrekar and M. Athawale, *Tetrahedron Lett.*, 2002, **43**, 4797–4800; (*c*) F. Aulenta, M. G. B. Drew, A. Foster, W. Hayes, S. Rannard, D. W. Thornthwaite and T. G. A. Youngs, *Molecules*, 2005, **10**, 8–97.

11 H. Kamogawa, Y. Haramoto, T. Nakazawa, H. Sugiura and M. Nanasawa, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 1577–1578; R. M. Boden, W. L. Schreiber, F. Tabak and H. G. M. Reijmer, US 6165452, 2000.

12 R. Suffis, M. L. Barr, K. Ishida, K. Sawano, T. Sato and A. G. van Loveren, *World Pat.*, WO 94/06441, 1994; A. Harriman, *Angew. Chem., Int. Ed.*, 2007, **46**, 5836–5863.

13 D. M. Clode, *Chem. Rev.*, 1979, **79**, 491–513.

14 E. Neuzil, J. Josselin, J. C. Breton, J. L. Gaumet and B. Lemanceau, *Bull. Soc. Pharm. Bordeaux*, 1979, **118**, 82–90; P. M. Lukin, A. B. Zolotoi, S. V. Konovalikhin, S. P. Zil'berg, A. Kh. Bulai, O. A. D'yachenko, L. O. Atovmyan and O. E. Nasakin, *Russ. Chem. Bull.*, 1986, **35**, 1318–1319; J. F. Miller and A. Spaltenstein, *Tetrahedron Lett.*, 1996, **37**, 2521–2524.

15 H. Q. N. Gunaratne, P. Nockemann and K. R. Seddon, *Green Chem.*, 2014, **16**, 2411–2417; M. Blesic, H. Q. N. Gunaratne, J. Jacquemin, P. Nockemann, S. Olejarz, K. R. Seddon and C. R. Strauss, *Green Chem.*, 2014, **16**, 4115–4121.

16 M. D. Soutullo, R. A. O'Brien, K. E. Gaines and J. H. Davis Jr., *Chem. Commun.*, 2009, 2529–2531.

17 K. Laumen and M. P. Schneider, *Chem. Commun.*, 2009, 598–600; K. Powell, J. Benkhoff, W. Fischer and K. Fritzsche, *Eur. Coat. J.*, 2006, **9**, 40–49.

18 S. J. Coles and P. A. Gale, *Chem. Sci.*, 2012, **3**, 683–689.