Utilization of pyridoxal acetal salts as water-triggered, slow-release pro-fragrances

Journal:	*New Journal of Chemistry*
Manuscript ID	NJ-LET-06-2018-003229.R1
Article Type:	Letter
Date Submitted by the Author:	12-Jul-2018
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Journal Name

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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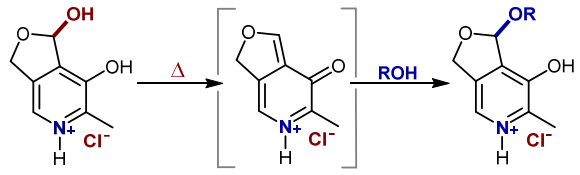
The synthesis of pyridoxal acetal salts and the controlled-release of the alcohols in the presence of neutral pH water is described. The rate of release was monitored by ^{1}H NMR and was found to be dependent on the concentration of water in the sample. The acetal salts are stable in the absence of moisture and show promise as a vitamin-based pro-fragrance delivery system.

Volatile organic compounds (VOCs) function as signaling compounds in nature and are utilized in a myriad of everyday items including personal care products, detergents, and perfumes. The ability to preserve a fragrance for a long period of time while allowing for its continued release is challenging due to the efficient evaporation of these molecules. The delivery of VOCs in consumer products is commonly accomplished by encapsulation in designed matrices and polymers or in oil-in-water emulsions in order to preserve the longevity of the fragrance.[1] These physical release systems rely on slow diffusion or via the breaking or dissolving of a capsule.[2] A drawback of the polymer systems is the low mass economy and typically low biodegradability.[3] Cyclodextrin derivatives have also been studied for fragrancy delivery; however their utility is limited by high substrate specificity.[4]

An alternative approach for the controlled delivery of VOCs is via chemical release using a class of compounds called pro-fragrances.[1] In these systems, a non-volatile substrate is covalently bound to a target molecule and selectively cleaved in the presence of a specific stimuli. In consumer products, the VOC release must occur under mild conditions, usually thermally, photochemically, or enzymatically.[1] Fragrant alcohols have been delivered as pro-fragrance esters that release in the presence of a lipase enzyme[5] or when exposed to a high pH.[6] Davis and Hermann independently illustrated that dynamic equilibrium hemiacetal systems could be used for the slow-release of volatile alcohols in aqueous media.[7] Recently, Gunaratne and coworkers developed an ionic liquid class of materials that release fragrant alcohols from stable hemiacetals in the presence of neutral water.[8] This is noteworthy as it could likely respond to atmospheric humidity or perspiration which would make it useful in personal care products. While this was a significant development, the potential toxicity of ionic liquids and their impact on the environment affects the viability of this chemical delivery system.[9,10] To address these limitations, we sought to develop a bio-based pro-fragrance that could also be triggered by neutral water from a benign vitamin scaffold.

Vitamin B_6 is an essential nutrient consisting of several vitamers including pyridoxal, pyridoxine, pyridoxamine, and their phosphorylated derivatives. While pyridoxine HCl is the most common form of the vitamin B_6 complex found in dietary supplements and in treatments for various skin conditions, pyridoxal 5'-phosphate is the active form of the vitamin.[11] The vitamers of vitamin B_6 can interconvert in biological systems to generate pyridoxal 5'-phosphate, which is a cofactor in over 100 enzyme-catalyzed reactions involved in metabolism and regulatory functions.[11] Herein, we report the utilization of pyridoxal acetal salts as vitamin-based pro-fragrances that release target molecules possessing an alcohol moiety in the presence of water at neutral pH. This delivery system conforms to the desired traits of chemical delivery systems with respect to precursor stability, biodegradability, and cost efficiency as described by Herrmann.[1]



1 pyridoxal HCl — **2** *ortho*-pyridinone methide — **3** acetal

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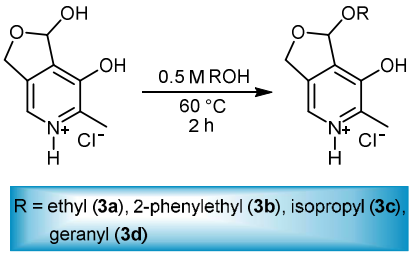
Electronic Supplementary Information (ESI) available: Detailed procedure for the synthesis of the pyridoxal acetal salts, characteristic data, NMR spectra (^{1}H and ^{13}C) of the products, and NMR stack plots used in the NMR time-dependent studies. See DOI: 10.1039/x0xx00000x

Scheme 1. Pyridoxal acetal generation via a secondary *ortho*-pyridinone methide intermediate.

Pyridoxal HCl and pyridoxine have been known to undergo *ortho*-pyridinone methide chemistry for decades;[12] however, this reactivity has received little attention.[13] Recently, we reported a study on the catalyst-free, regioselective etherification of pyridoxine,[14] although the reaction requires long reaction times and high temperatures. While commonly drawn as the aldehyde tautomer, pyridoxal HCl exists as the furopyridine **1** as illustrated in Scheme 1. This tautomer enables pyridoxal HCl to undergo *ortho*-pyridinone methide formation to form **2** under mild conditions due to the stability imparted by the dihydrofuran moiety when compared to the primary alcohol of pyridoxine. Once the *ortho*-pyridinone methide **2** is generated, the oxa-Michael addition of the alcohol occurs to provide the pyridoxal acetal salt **3**.

A series of conditions was screened to determine the optimal parameters for the reaction and to avoid the need for purification. Exposing pyridoxal HCl to the desired alcohol at 60 °C in the absence of catalyst provided clean conversion to the acetal in high yields as illustrated in Scheme 2.[15] For volatile alcohols, the solvent was evaporated to provide analytically pure product, **3a** and **3c**. Geraniol and 2-phenylethanol were selected as substrates due to their use as fragrances in industry. With respect to these higher boiling point fragrant alcohols, dry diethyl ether was added to the reaction mixture to precipitate the acetal that was then isolated by vacuum filtration. The fragrant alcohols can be recovered by evaporation of the diethyl ether.



Scheme 2. Synthesis of pyridoxal acetals **3a**-**3d**.

The hydrolysis of the target alcohol from the pyridoxal acetal salt was monitored in the presence of D_2O by ^1H NMR spectroscopy. DMSO-d_6 was chosen as the solvent for the kinetics study since it is miscible with water which ensures accurate monitoring of the acetal cleavage. Since the hydrolysis produces no discernible byproducts, the hydrolysis can be monitored by comparing the formation of hemiacetal C-H peak to the loss of the acetal C-H peak.[15] For substrate **3a**, the integration of the acetal C-H peak at 6.58 ppm was compared to the integration of the pyridoxal hemiacetal C-H peak at 6.41 ppm hourly to determine conversion. A stack plot of the NMR spectra for 50% D_2O solution in DMSO-d_6 over 20 hours is illustrated in Figure 1.[15]

To determine the kinetics of the hydrolysis with respect to the concentration of water, acetal **3a** was exposed to varying concentrations of D_2O. The release of ethanol from **3a** was measured at concentrations of 25%, 35%, 50%, and 100% D_2O in DMSO-d_6 and is plotted in Figure 2. The plot demonstrates that the rate of release of ethanol increases with higher concentrations of D_2O. The 100% D_2O trial provides full cleavage after 10 hours whereas a lowest concentration of D_2O (25%) provides the slowest release with only 28% of the acetal cleaved to pyridoxal after 25 hours. The 50% D_2O trial provided 74% release and the 35% D_2O trial provided 42% release after 25 hours. The slow release of the volatile alcohol, even in the presence of high concentrations of water, is significant as it allows for these acetals to function as vitamin-based pro-fragrances providing longevity to the attached fragrant alcohols. Additionally, the acetals can be stored in a freezer for more than 6 months with no decomposition or cleavage.

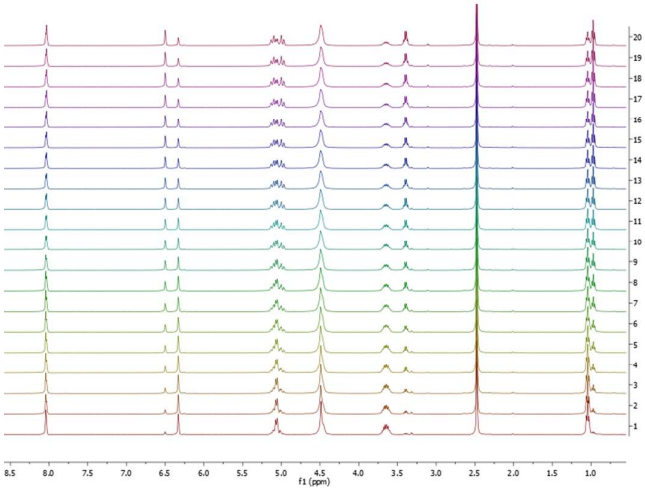


Figure 1. A stack plot of ^1H NMR spectra (x-axis) per hour (y-axis) demonstrating the release of ethanol in the presence of deuterium oxide at a concentration of 0.2 M in DMSO-d_6/D_2O (50:50; v/v) at 23 °C.

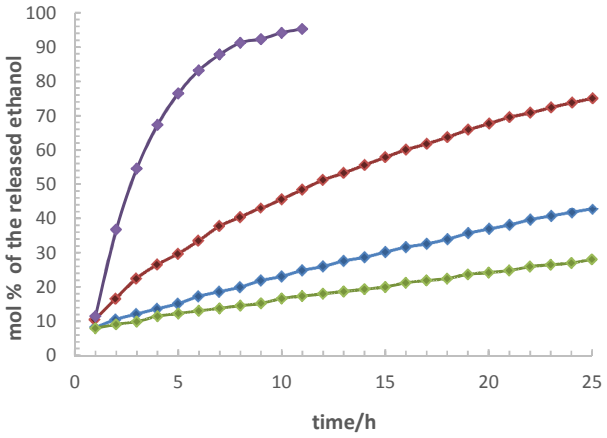


Figure 2. Kinetic reaction profile for the release of ethanol from **3a** at varying concentrations in DMSO-d_6/D_2O at 23 °C. The D_2O concentrations are 25% (green), 35% (blue), 50% (red), and 100% (violet).

The rate of release for ethanol, isopropanol, 2-phenylethanol, and geraniol were monitored at a 0.2 M concentration of 30% D_2O in DMSO-d_6 from the respective pyridoxal acetal. Each acetal demonstrated linear controlled-release with ethanol providing the slowest release at 30% and isopropanol providing the highest release of 37% after 22 hours. In all cases, the acetals hydrolyze to the target molecule and pyridoxal HCl quantitatively. Since other fragrance delivery systems can lose material in side reactions,[8] the high fidelity in the release for these alcohols is significant.

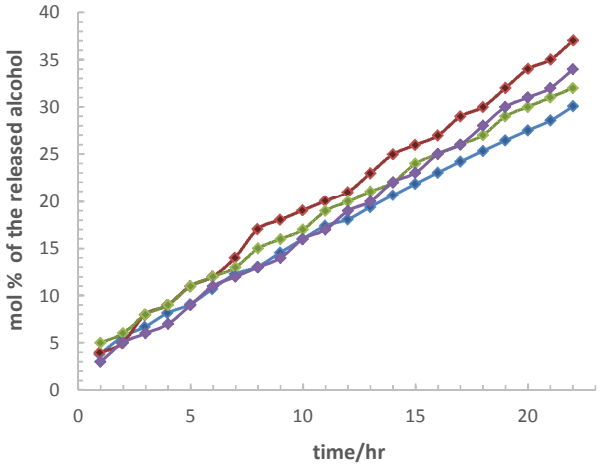


Figure 3. Time-dependent release of ethanol (blue), 2-phenylethanol (green), isopropanol (red), geraniol (purple) from the pyridoxal acetal salts **3a**–**3d** in 0.2 M DMSO-d_6/D_2O (70:30; v/v) at 23 °C.

This report describes a high-yielding, one-step synthesis of the pyridoxal acetal salts and demonstrates their function as cost-effective, bio-based materials for the slow release of alcohols in the presence of water at neutral pH. The rate of release was determined to be proportional with the concentration of water in time-dependent ^{1}H NMR studies. Each acetal provided controlled-release with no discernible loss of fidelity to side reactions over a 22-hour period. We believe this chemical delivery system could find utility in a wide range of applications including personal care products where perspiration could trigger the fragrance release.

The project described was supported by Award No. CHE-1530959 from the National Science Foundation. GRB and KLM are grateful for the generous support of the Seidler Fellowship administered by the College of Arts and Sciences at FGCU.

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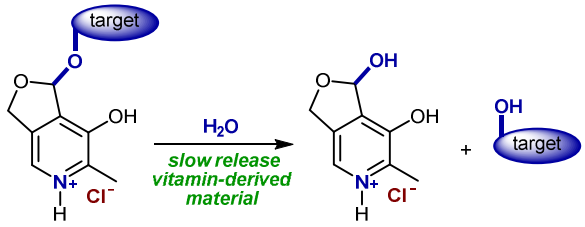
15 See the Supporting Information for experimental yields, reaction procedures, a more detailed explanation of the hydrolysis monitoring by NMR, and the remainder of the NMR stack plots.



The use of vitamin B_6 derivatives as a chemical delivery system for volatile alcohols initiated by neutral water is described.