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Application of acetone acetals as water scavengers and derivatization agents prior to the gas chromatographic analysis of polar residual solvents in aqueous samples

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ABSTRACT

The sensitivity of gas chromatography (GC) combined with the full evaporation technique (FET) for the analysis of aqueous samples is limited due to the maximum tolerable sample volume in a headspace vial. Using an acetone acetal as water scavenger prior to FET-GC analysis proved to be a useful and versatile tool for the analysis of high boiling analytes in aqueous samples. 2,2-Dimethoxypropane (DMP) was used in this case resulting in methanol and acetone as reaction products with water. These solvents are relatively volatile and were easily removed by evaporation enabling sample enrichment leading to 10-fold improvement in sensitivity compared to the standard 10 μL FET sample volumes for a selection of typical high boiling polar residual solvents in water. This could be improved even further if more sample is used. The method was applied for the determination of residual NMP in an aqueous solution of a cefotaxime analogue and proved to be considerably better than conventional static headspace (sHS) and the standard FET approach. The methodology was also applied to determine trace amounts of ethylene glycol (EG) in aqueous samples like contact lens fluids, where scavenging of the water would avoid laborious extraction prior to derivatization. During this experiment it was revealed that DMP reacts quantitatively with EG to form 2,2-dimethyl-1,3-dioxolane (2,2-DD) under the proposed reaction conditions. The relatively high volatility (bp 93 °C) of 2,2-DD makes it possible to perform analysis of EG using the sHS methodology making additional derivatization reactions superfluous.

1. Introduction

Analysis of aqueous samples with gas chromatography (GC) has always been a challenge mainly due to water intolerance of most stationary phases towards repetitive injections of high amounts of water and injection liners that are incompatible towards the introduction of large amounts of water. Standard GC-columns often degrade and injection liners are not able to deal with the gas expansion of water because of the heated injection port. Developed methods for the analysis of aqueous samples are either based on the isolation and enrichment of analytes prior to GC separation or on direct aqueous injections using special retention gaps and/or columns. Isolation of analytes can be done by using techniques such as supercritical fluid extraction (SFE), subcritical water extraction (SWE), cloud point extraction (CPE), solid phase extraction (SPE), solid phase microextraction (SPME), stir-bar sorptive extraction (SBSE) and single drop microextraction (SDME). However, all these techniques are biased towards more volatile compounds or apolar compounds that have a rather low affinity for water. Recently, a method was developed that uses a split injector packed with an adsorbent containing LiCl to enable injections up to 100 μL for the analysis of several high boiling analytes in water [1]. For the analysis of residual solvents in aqueous or water soluble pharmaceutical products, static headspace (sHS) GC and dynamic headspace (DHS) GC are traditionally used [2]. HS analysis is, in contrast to direct injection, a very clean method of introducing analytes on a GC column. When performing HS techniques with aqueous samples, incubation temperatures should be kept relatively low to ensure that the HS pressure does not exceed the limitations of the instrument. This limitation restricts the sensitivity for analytes with a high affinity for water and high boiling points such as *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), dimethylsulfoxide (DMSO), *N*-methylpyrrolidone (NMP) and 1,2-dimethylimidazole (DMI) when sHS is used. Their determination as residual solvents in aqueous samples is really problematic. A work around for DMSO is its reduction to the more volatile

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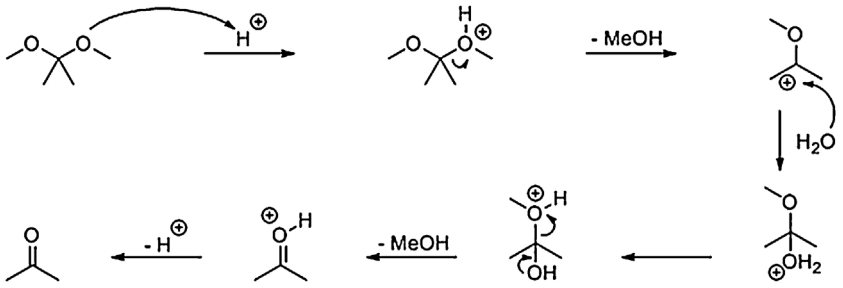

Fig. 1. Acid catalysed hydrolysis of DMP to produce methanol and acetone.

dimethylsulfide (DMS) enabling the indirect quantitative analysis of this high boiling polar solvent [3]. An additional possible disadvantage is that HS sampling is known to suffer from matrix effects. The so-called Full Evaporation Technique (FET) in combination with a more water resistant column has proven to be useful to improve the sensitivity for these typical polar residual solvents in aqueous samples [4] and provides elimination of matrix effects [5]. However, as with sHS sampling, pressure limits have to be respected as well, meaning that the introduced sample volume and therefore the sensitivity is still limited for aqueous samples. An approach to avoid this problem is to use desiccants such as $CaCl_2$ or K_2CO_3 to trap water inside a HS vial forming hydrates. A method described in literature uses 6.0 g of $CaCl_2$ to remove water for the analysis of phenol [6]. However, $CaCl_2$ is known to adsorb phenol [7] and might introduce unwanted matrix effects for other analytes too. Furthermore, introducing 6.0 g of a desiccant in a vial has serious consequences for the partial pressures of the analytes present in the vial. Moreover, water can be released when higher HS temperatures are used for the evaporation of higher boiling analytes. When performing this described method in our lab, most sample vials (~75%) actually ruptured for unclear reasons. Rupturing of the sample vials occurred in the incubation oven of the HS sampler, but when the heating process was repeated in an ordinary oven, vials stayed intact. Recently, FET has been combined with DHS to increase the tolerable sample volume by transferring the whole sample over a Tenax® filled trap thereby eliminating the water [8–10]. Transferring occurs by purging the sample vial until analytes are (nearly) completely transferred to the trap. However, problems could still exist with analytes such as ethylene glycol (EG) which is prone to interact with many parts of the instrument (injector, column, etc.) resulting in erroneous results. Often, EG or other diols are analysed as phenyl boronate (PBA) [11] or trimethylsilyl (TMS) derivatives [12–14]. Unfortunately, most GC derivatization reagents tend to react with water as well and are therefore not easily applicable to aqueous samples. Furthermore, the derivatization of EG with PBA leads to a product with an even higher boiling point than EG itself (2-phenyl-1,3,2-dioxaborolane, 218–220 °C) and is susceptible to hydrolysis in an aqueous environment [15].

An approach to circumvent the abovementioned problems could be a selective chemical reaction to remove enough or all water in order to be able to introduce a larger sample volume in a HS vial and enable derivatization and analysis of compounds such as EG; thereby increasing the sensitivity significantly when FET is applied. In fact, such chemical reactions are known including drying reactions with several agents or certain hydrolysis reactions such as the reaction of water with acetone acetals to give acetone and an alcohol as final products. This reaction has proven to be useful in the past for the analysis of DMSO in urine samples using direct injection in which 2,2-dimethoxypropane (DMP) was used as water scavenger [16]. DMP is also known as acetone dimethyl acetal and reacts endothermically with equimolar amounts of water producing methanol and acetone in a molar ratio of 2:1 with the help of an acid as catalyst (Fig. 1). The reaction consists of several equilibria with their own rate constants and starts by protonation of DMP resulting in methanol that splits off from the molecule. The resulting intermediate will react with a water molecule and lose a second methanol to form a protonated acetone molecule which yields a proton to catalyse further the reaction. This specific reaction has already been used before for the quantitative analysis of water when the well-known Karl–Fischer titration is not applicable [17–19]. Furthermore, samples have been dried using DMP prior to infrared (IR) spectroscopy [20], electron microscopy [21–23] and other histological applications [24,25]. It has been proposed in the past that a volumetric ratio of 1:10 for water:DMP is sufficient for complete water removal.

This work describes the optimization and application of this DMP reaction on the analysis of a selection of typical high boiling residual solvents in aqueous samples. Firstly, the reaction was used for sample enrichment to extend the applicability of FET for aqueous samples and was tested for the analysis of DMF, DMA, DMSO, NMP and DMI. The final method was used for the detection and quantification of NMP in an aqueous solution of an analogue of cefotaxime (cephalosporin antibiotic) which is typically used for intravenous injections. Furthermore, the reaction was used for the analysis of EG in water and contact lens solutions after DMP treatment in which EG forms a cyclic ether named 2,2-dimethyl-1,3-dioxolane (2,2-DD). Contact lens solutions of several suppliers were collected and analysed for EG using the described protocol. Contact lenses can be made sterile by using ethylene oxide which may form EG when it comes into contact with water. Residual EG that is exposed to a person's eyes can cause irritation. The short term exposure limit (STEL) of EG is reported to be 40 ppm according to European guidelines [26]. STEL is the maximum concentration of a chemical to which workers may be exposed continuously for a short period of time without any danger to health, safety or work efficiency.

2. Experimental

2.1. Reagents

Methanol (99.99%), *n*-propanol (99+%), EG (99.75%), DMP (98+%) and NMP (>99.5%) were obtained from Acros Organics (Geel, Belgium). DMP was further purified by distillation under a nitrogen atmosphere. Benzyl alcohol (BA, >99%), DMI (>99.99%) and LC–MS grade water were purchased from Sigma Aldrich (St. Louis, MO, USA); DMF (>99.99%), acetone (>99.99%) and triethylamine (99.5%) from Fisher Scientific (Loughborough, United Kingdom) and DMSO from Merck (Darmstadt, Germany). Hydrochloric acid (37.5%) (HCl) was bought from VWR International S.A.S. (Fontenay-sous-Bois, France). Formic acid (65%) and sodium carbonate were from Chem-Lab NV (Zedelgem, Belgium). 2,2-DD (>98%) was purchased from TCI Europe (Zwijndrecht, Belgium).