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Rapid and facile detection of four date rape drugs in different beverages utilizing proton transfer reaction mass spectrometry (PTR-MS)†

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In this work, we illustrate the application of proton transfer reaction mass spectrometry (PTR-MS) in the field of food and drink safety. We present proof-of-principle measurements of four different drinks (water, tea, red wine and white wine) each spiked separately with four different date rape drugs (chloral hydrate, tricholorethanol, γ-butyrolactone and butanediol). At first, the ideal PTR-MS operating conditions (reduced electric field strength and monitoring the most abundant [fragment] ion) for detection of the drugs were determined utilizing a time-of-flight-based PTR-MS instrument. We then dissolved small quantities of the drugs (below the activation threshold for effects on humans) into the various types of drinks and detected them using a quadrupole-based PTR-MS instrument via two different sampling methods: (1) dynamic headspace sampling and (2) direct liquid injection. Both methods have their advantages and drawbacks. Only with dynamic headspace sampling can rape drug contaminations be detected within a timeframe of seconds, and therefore, this method is the most promising use of PTR-MS as a fast, sensitive and selective monitor for the detection of food and drink contamination. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: PTR-MS; PTR-TOFMS; food safety; rape drug detection; contamination monitoring; drink spiking; proton transfer reaction

Introduction

Food and drink safety, drinking water security and security of the food chain from contaminations are hot topics, as exemplified in the recent FP7-SEC-2012-1 call of the European Commission. The detection of food and drink contaminants requires an instrument that is capable of monitoring compounds in real time, has a fast response, is highly selective and reliable. Furthermore, the instrument must be able to detect a broad range of chemical compounds. Proton transfer reaction mass spectrometry (PTR-MS) has all of these capabilities. In this article, we illustrate its potential for detecting so-called date rape drugs in various types of drinks. This opens up a new method for the fast detection of date rape drugs, which still causes major difficulties for established technologies.

PTR-MS is already well established in food and flavor research (e.g.[1–3]). In a recent review by Biasioli *et al.* [4] dealing with the applications of PTR-MS in food science and technology, they concluded that 'PTR-MS is an accurate, highly sensitive, direct-injection technique that allows for the rapid characterization of food products and for the monitoring of processes in food science and technology, and agro-industry, without any pre-treatment'.[4] Thus, although we are concentrating in this article on a special class of contaminants in drinks, the work of Biasioli *et al.* implies that PTR-MS can also be used for the analysis and quantification of other contaminants in food and beverages. This present study follows on from our recent PTR-MS investigations dealing with dangerous and/or illicit substances such as chemical warfare agents [5] and illicit and controlled prescription drugs.[6]

Date rape drug is a rather colloquial expression for any kind of substance that can be administered to an unknowing victim to disable a person's resistance against sexual abuse. Sometimes, these substances are also used to knock out and subsequently rob a person. Regardless of the purpose, two major classes of drugs are commonly used: (1) hypnotics and (2) γ-hydroxybutyric-acid-related compounds.[7] As representatives for class 1, we chose chloral hydrate ($C_2H_3Cl_3O_2$, 2,2,2-trichloroethane-1,1-diol, CH) and trichloroethanol ($C_2H_3Cl_3O$, 2,2,2-trichloroethanol, TCE). Chloral hydrate is one of the oldest sedatives/hypnotic drugs,[8] and because of its various uses, e.g. in microscopy and in the preparation of rodenticides, it is easily available to criminals. CH is often used in sleeping pills, where typical doses are about 500 mg (e.g. Chloraldurat 500, G. Pohl-Boskamp GmbH & Co., Germany). CH is quickly metabolized to TCE in the human body,[9] with this metabolite having a very similar pharmacological effect as CH. However, TCE is in many countries not a controlled substance and therefore also readily available.

γ-Hydroxybutyric acid ($C_4H_8O_3$, 4-hydroxybutanoic acid, GHB) is an illegal or at least regulated drug in most countries. Although it possesses some therapeutic uses, from treating narcolepsy to

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supporting alcohol addicts during withdrawal,[10] GHB is known to the broad public mainly as a recreational drug under the popular name *liquid ecstasy*. Only about 1.5 to 2.5 g of GHB is required to cause euphoric effects. Above those levels, unconsciousness and even coma may result after several minutes.[11] However, due to the illegal status of GHB, its importance as an intoxicant is decreasing, especially as two substitutes are readily available. γ-Butyrolactone ($C_4H_6O_2$, dihydrofuran-2(3H)-one, GBL) and 1,4-butanediol ($C_4H_{10}O_2$, butane-1,4-diol, BDO) are both metabolized to GHB within the human body. GBL is converted by serum and liver lactonases to GHB,[12] whereas BDO undergoes alcohol dehydrogenase.[13] These lead to very similar effects for the drug consumer regardless of which of the three substances was ingested.[14] It has to be noted that due to the higher bioavailability of GBL, the knockout dose is somewhat lower than for GHB, i.e. about 2 ml of GBL can induce a comatose state within minutes.[11] GBL and BDO are important industrial compounds and therefore are not treated as illegal drugs in most countries, provided that they are not sold for human consumption. Typical containers of 2.5 l high-purity GBL or BDO (sufficient amount for about 2000 "trips") can be bought from most chemical suppliers for less than EUR 100 making these substances probably the cheapest and most easily available intoxicants of all.

The most commonly used analytical technique for detecting such rape drug compounds is gas chromatography (GC).[15] However, alternative analysis methods are available including liquid chromatography,[7] ion mobility spectrometry,[16] capillary electrophoresis,[17] test strip cards,[17] selected ion flow tube,[18] etc. These technologies have various specific problems (e.g. low selectivity, long response/analysis times, limited sensitivity, etc.). In comparison, PTR-MS has the potential of providing a fast, reliable, highly sensitive and very simple detection method.

Experimental setup

For this study, we utilized two IONICON Analytik GmbH (Austria) PTR-MS instruments, namely a quadrupole mass filter and a time-of-flight (TOF)-based type. The latter one is a PTR-TOF 8000 with high sensitivity (approximately 150 cps/ppbv) and high mass resolution of up to 8000 m/Δm,[19] whereas the quadrupole instrument is a high-sensitivity PTR-MS with a sensitivity of several hundred cps/ppbv and a detection limit in the ppqv (parts per quadrillion) range.[20] The PTR-TOF 8000 was used to investigate the pure samples to determine the nature of the product ions via their exact masses. For the detection measurements, we used the quadrupole-based instrument. It has to be mentioned that both instruments are equipped with an identical PTR part so that the ionization conditions are directly comparable.

The PTR-MS technology itself is already well established and documented.[21] Briefly, water vapor, originating from a reservoir filled with distilled water, enters a hollow cathode ion source where it is transformed to H_3O^+ at very high purity levels of over 99%, thus making a mass filter for preselecting the primary ions obsolete. The H_3O ions subsequently enter the adjacent drift tube where the actual proton transfer takes place between the H_3O^+ and any molecule that possesses a higher proton affinity than water under the influence of a uniform electric field E that can be varied between 30 and 100 V cm^{-1}. One of the various advantages of such a setup is that no sample preparation is necessary, i.e. air containing traces of the sample molecules is continuously drawn into the instrument and analyzed virtually in real time (response times of about 100 ms). This feature is especially important when using PTR-MS as a continuous monitor for specific compounds such as contaminants in the field of food and drink safety.

In addition to using a direct inlet system, we have also utilized in this study a newly developed direct aqueous injection (DAI) inlet system, which we introduced in [22] and successfully applied to the detection of explosives traces in water in.[23] The DAI system allows us to sample liquids directly rather than just sampling their headspace. As we will demonstrate, this has advantages, but it comes at the expense of real-time detection. In the DAI version used for this study, an airstream is generated by a membrane pump, filtered in a zero air generator, dried in a Peltier cooler, regulated by a mass flow controller and subsequently heated in a thermostatic heating box. The tip of a gastight syringe filled with the liquid containing the trace compounds is placed in this airstream through a standard septum that seals the injection area from the environment. Low injection rates (below 0.1 μl/s) and high gas flows (above 1 l/min) in conjunction with elevated temperatures (above 60 °C) ensure the complete evaporation of the liquid. This DAI system can be coupled to every standard PTR-MS instrument via a T-piece (with one end open to the overflow and another to the PTR-MS instrument which typically samples at a rate of 50–500 sccm).

All chemicals were bought from Sigma-Aldrich (Austria) in the following purities: BDO >99%, CH >98%, GBL >99%, TCE >99%, and used without any further pretreatment. For the detection tests, the substances were mixed in water, tea made from common tea bags, red wine and white wine.

Results and discussion

Pure substances

To determine the best operating conditions and which product ions should be monitored, we started our study by investigating the pure substances. Small amounts of the compounds were put in glass vials sealed with polytetrafluoroethylene-coated septa. Air purified by a charcoal filter was drawn through these vials and subsequently introduced into a PTR-TOF 8000 instrument via polyether ether ketone lines. The samples were kept at room temperature. Figure 1 provides a summary of the (unnormalized) product ion intensities as a function of the reduced electric field (the ratio of electric field *E* to gas number density *N*; *E/N* is the main parameter that can be varied in PTR-MS investigations).

The protonated parent ion for CH is clearly detected on 164.881 *m/z*, but this is not the most abundant product ion (Fig. 1a). If the protonated parent ion is solely used for detection of CH, it turns out that the highest yield can be obtained between 120 and 150 Td. At 146.915 *m/z*, we see a fragment product ion which we assign to the loss of H_2O from protonated CH, i.e. $C_2H_2Cl_3O^+$. At a similar intensity, at least for slightly elevated *E/N* values, we detect a fragment on mass 130.946 *m/z*. We suggest that this corresponds to the loss of H_2O_2, i.e. resulting in $C_2H_2Cl_3^+$. The loss of OH and Cl leads to 112.937 *m/z*, which we see at higher *E/N* values at an increased intensity of about one order of magnitude. However, by far, the most abundant product ion at all *E/N* values is detected at 82.935 *m/z*, which can be assigned to $CH_4ClO_2^+$, i.e. the loss of CCl_2 from the protonated parent. From these measurements, we conclude that the best operating conditions for detecting CH are above 120 Td.

The results for TCE are presented in Fig. 1b. As found for CH, the non-dissociative proton transfer pathway occurs, which for

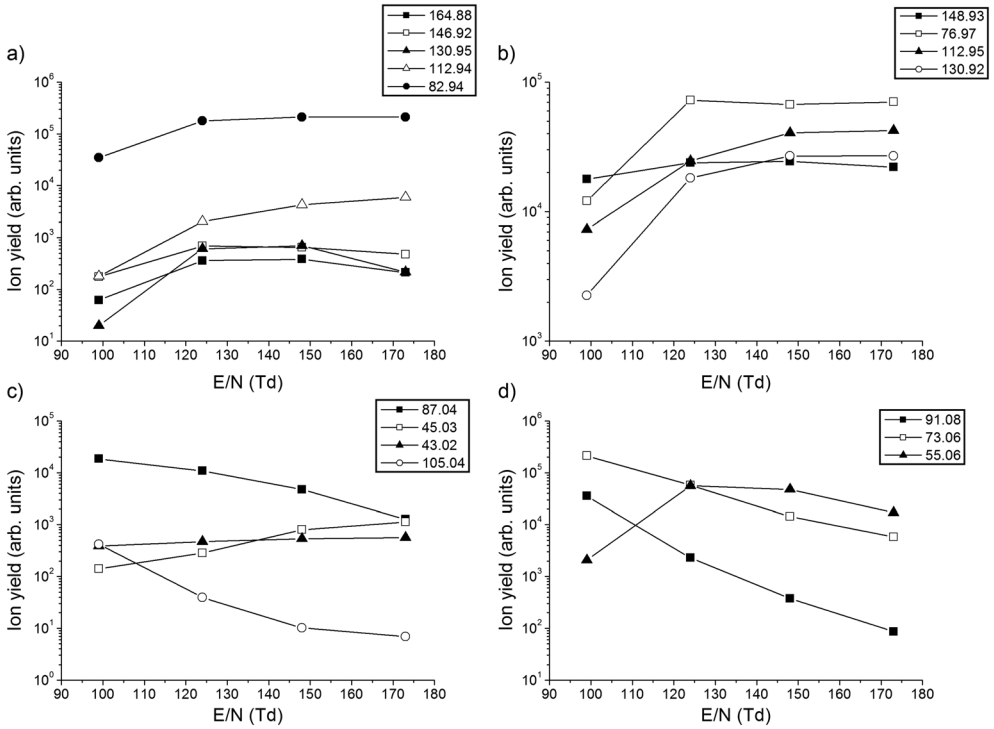

Figure 1. Resulting ion yields on a PTR-TOF 8000 for the protonated parent and fragment ions at different *E/N* settings. The substances were used in pure form: (a) CH, (b) TCE, (c) GBL and (d) BDO.

TCE results in an ion at 148.932 *m/z* and with an intensity being practically independent of the *E/N* used. The intensities for the product ions $[TCE\text{-}H_2O]H^+$ ($C_2H_2Cl_3^+$; 130.917 *m/z*) and $[TCE\text{-}HCl]H^+$ ($C_2H_3Cl_2O^+$; 112.954 *m/z*) increase with increasing *E/N* until a constant ion yield occurs at approximately 120 Td. However, at low *E/N*, the intensities of these product ions are insignificant to that observed at 76.974 *m/z*, which we assign to $C_2H_2OCl^+$ resulting from dissociative proton transfer following a loss of H_2Cl_2 from the protonated compound.

At the lowest *E/N* value used, the most abundant ion for GBL is the protonated parent at 87.044 *m/z*. A small signal corresponding to $C_4H_6O_2^+.H_2O$ is present at 105.040 *m/z* at very low intensities. The fragment ions at 45.030 *m/z* and 43.020 *m/z*, which we propose are $C_2H_5O^+$ and $C_2H_3O^+$, respectively, are observed only at elevated *E/N* values, i.e. above 150 Td. However, the best operating conditions for a sensitive detection of GBL appear to be at very low *E/N* values of about 100 Td.

The protonated parent ion for BDO is detected at 91.075 *m/z* at the lowest possible *E/N* value (Fig. 1d). The loss of H_2O leads to 73.064 *m/z*, which is the most abundant product at about 100 Td. At slightly higher *E/N* (between 125 and 225 Td), we detect another dominant product at 55.055 *m/z*. We propose that this is $C_4H_7^+$, i.e. the loss of $2(H_2O)$.

From the above studies of the pure compounds, we can select which ions to monitor and at which *E/N* values to maximize the detection sensitivity of the various rape drugs. These results are summarized in Table 1. It should be noted that in case the environment (drink) in which the drugs have to be detected contains substances that are overlapping or masking the ions mentioned in Table 1 (especially in case a quadrupole-based instrument with unit mass resolution is used), it could be preferable to use one of the characteristic fragments. However, we did not experience this problem for the four drinks investigated in the present study.

Table 1. Product ions, *m/z* values to be monitored and reduced electric field strengths for the most sensitive detection of the four date rape drugs

Substance	Mass (*m/z*) monitored	*E/N* (Td)
CH	82.990	125
TCE	76.979	125
GBL	87.044	100
BDO	73.064	100

Drink analysis—headspace

Concentrations of about 30 ppmw for CH, TCE, GBL and BDO in plain water, tea, red wine and white wine were prepared. This mixture ratio represents a dose far below the thresholds where any effect would be noticed by someone consuming such a spiked drink (e.g. 30 µl of GBL in 1 l of plain water, whereas the first mild effects would occur only at 500 µl).[11]

The headspace measurements were performed utilizing the same setup as described in the previous section, with the pure substances being replaced by the mixtures and the PTR-TOF 8000 being replaced by a high-sensitivity PTR-MS. The reason for this instrumental change was that we wanted to figure out if the drugs could be detected in a rather complex environment even without the help of the high mass resolution of a PTR-TOF 8000. At first, the four liquids (water, tea, red wine and white wine) were analyzed in the absence of any spiking, and the resulting ion yields on the corresponding *m/z* positions were then subsequently subtracted from the results obtained from the mixtures (the background ion yields on the nominal masses were in the range of 0.1% to 10% of those of the spiked drinks).

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Based on the findings from the investigations of the pure substances, we chose the parameters listed in Table 1 for monitoring for date rape drug contamination.

Figure 2 provides a summary of the measurements. Although the same concentrations of the date rape drugs were placed in the various drinks, there is a variation in the ion signal intensities.

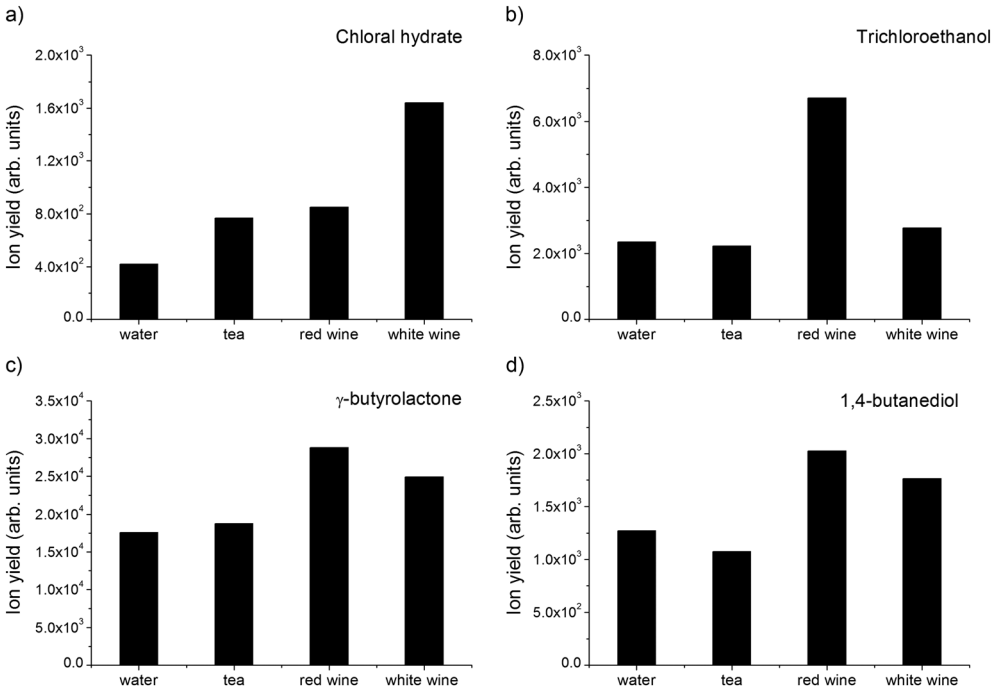

Figure 2. Results of the dynamic headspace measurements of CH, TCE, GBL and BDO in four different liquids: (a) plain water, (b) tea, (c) red wine and (d) white wine. For all substances, the concentration of the mixture was about 30 ppmw. The *E/N* values and the monitored masses were chosen as listed in Table 1. The error of measurement is estimated to be about 5%.

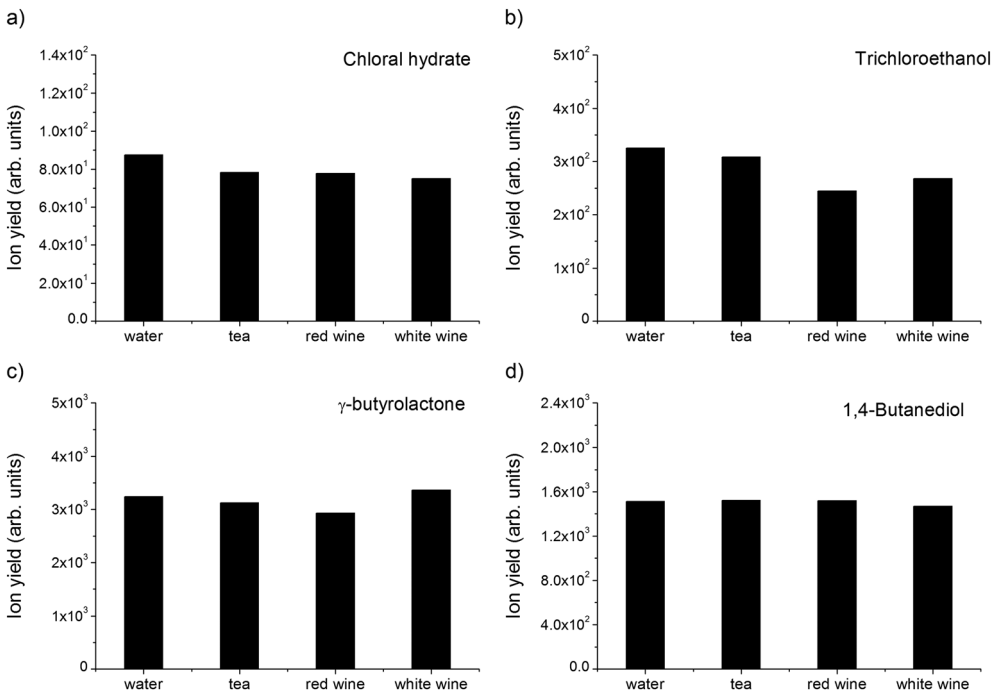

Figure 3. Results of the direct aqueous injection measurements of (a) water, (b) tea, (c) red wine and (d) white wine containing 30 ppmw of the respective rape drug (CH, TCE, GBL and BDO). The *E/N* values and the monitored masses were chosen as listed in Table 1. The error of measurement is estimated to be about 10%.

However, taking into account that the four liquids are different matrices (composition, pH value, traces of carbonic acid, etc.), the same headspace concentrations will not occur.

Importantly, we have demonstrated that independent of the type of drink, all four date rape drugs in low concentrations can be easily and rapidly detected with PTR-MS at very high signal intensities. As the dwell times for every point in the measurement were about 2 s, the method proves to be extremely fast in comparison with, e.g. the established method of GC/MS.

Drink analysis—DAI inlet system

Finally, we investigated the four dilutions presented in the last section with our DAI inlet system coupled to a high-sensitivity PTR-MS instrument. The PTR-MS settings were again those presented in Table 1. For each data point, the liquid was filled into a syringe, which was inserted into the DAI system. After starting the injection, we waited for stable conditions (around 20 s to several minutes) and took an average of about 3 min integration time. Again, at first, the liquids were analyzed without any drugs mixed into them, and the ion yields on the corresponding *m/z* ratios were subtracted from the ones obtained from the spiked drinks.

As one would expect from a liquid injection method, the obtained ion yields (Fig. 3) are much more consistent between liquids than for the dynamic headspace measurements. In fact, the standard deviations are well below 10%, which can be assigned to the measuring error [consisting of statistical errors, errors of the different DAI components (flow controller, syringe pump, temperature sensors) and errors of the PTR-MS components (pressure gauges, pressure controller, etc.)]. Figure 3 provides a summary of the measurements. However, this improvement in consistence of the signal intensities in different liquids is at the expense of a highly prolonged response time (from single seconds to minutes). Therefore, there is little advantage in using a DAI system for the four rape drugs in this study. It would, however, be of greater use for the detection of substances which possess a high Henry constant or are somehow bound to the liquid's matrix, i.e. are only present in very low concentrations in the headspace.

Summary and conclusions

We analyzed four readily available date rape drugs (CH, TCE, GBL and BDO) using a high mass resolution TOF-based PTR-MS instrument. Based on the outcome of that analysis, we determined the best operating conditions (*E/N* value and most abundant ion) for every compound to provide the best possible sensitivity for detecting the substances in different drinks. By producing mixtures of date rape drugs in four different common liquids (water, tea, red wine and white wine) in concentrations far below that used to "spike" drinks, we illustrated that all of the drugs could be easily detected in all liquids by either head space analysis at room temperature or via a DAI system. Dynamic headspace sampling has the advantage of providing a short response time (seconds), whereas the advantage of the slower DAI method lies mainly in the independence of the measured signal intensity and the matrix. Although the detection measurements were performed utilizing a quadrupole-based PTR-MS instrument (with unit mass resolution), we did not experience any overlapping problems from compounds present in the different drinks. However, to reach an even higher level of confidence, a high mass resolution PTR-TOFMS instrument could be used.

We conclude that PTR-MS can be used as a fast analytical device for determining whether a drink has been spiked with a date rape drug with a high level of confidence. Taking into account our recent publications dealing with the detection of illicit drugs,[6] chemical warfare agents [5] and explosives,[23] we have demonstrated that PTR-MS is a very valuable broad-based analytical technology for the extremely fast and nearly unambiguous (because of the high mass resolution and characteristic fragmentation patterns) detector of threat agents and in this article for drink contamination. Examples for institutions benefiting from these advantages would be forensic laboratories or police stations. There a PTR-MS instrument could verify extremely fast (compared with, e.g. GC/MS, which is highly selective but slow) and at high confidence levels (compared with test strips, which are rather fast but not very selective) if a suspicious drink has been spiked with a drug or not. In addition, the instrument would not be limited to this application but could also be used for the identification of any suspicious solids, liquids or gases (if they are illegal drugs, precursor chemicals, explosives, toxic compounds or harmless everyday substances).

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