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Headspace analysis of new psychoactive substances using a Selective Reagent Ionisation-Time of Flight-Mass Spectrometer

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ABSTRACT

The rapid expansion in the number and use of new psychoactive substances presents a significant analytical challenge because highly sensitive instrumentation capable of detecting a broad range of chemical compounds in real-time with a low rate of false positives is required. A Selective Reagent Ionisation-Time of Flight-Mass Spectrometry (SRI-ToF-MS) instrument is capable of meeting all of these requirements. With its high mass resolution (up to $m/\Delta m$ of 8000), the application of variations in reduced electric field strength (E/N) and use of different reagent ions, the ambiguity of a nominal (monoisotopic) m/z is reduced and hence the identification of chemicals in a complex chemical environment with a high level of confidence is enabled. In this study we report the use of a SRI-ToF-MS instrument to investigate the reactions of H_3O^+, $O_2{}^+$, NO^+ and Kr^+ with 10 readily available (at the time of purchase) new psychoactive substances, namely 4-fluoroamphetamine, methiopropamine, ethcathinone, 4-methylethcathinone, N-ethylbuphedrone, ethylphenidate, 5-MeO-DALT, dimethocaine, 5-(2-aminopropyl)benzofuran and nitracaine. In particular, the dependence of product ion branching ratios on the reduced electric field strength for all reagent ions was investigated and is reported here. The results reported represent a significant amount of new data which will be of use for the development of drug detection techniques suitable for real world scenarios.

1. Introduction

The abuse of drugs is an important issue affecting today's society. Although many drug species are controlled by law, a market for new psychoactive substances (i.e. legal highs, research chemicals, and designer drugs) which are not controlled by drug legislation, has recently emerged. These readily available drugs are increasingly being used as substitutes for prohibited drugs, especially by those who are looking for a high, but who do not wish to commit a criminal act [1].

A review of the current literature shows that most new psychoactive substances have received little scientific interest, especially substances new to the market. For many of these compounds the only up-to-date source of information (e.g. synthesis, purity, side-effects, etc.) is to be found online in user forums [2,3] and no data on properties like proton affinity, ionisation energy, etc. are available. As new psychoactive substances regularly enter the market, it is important that broad-based analytical methods exist which have the ability to rapidly detect them, without the need for major changes in operational procedures. This rapid identification is especially important if a user has taken an unidentified drug and requires urgent medical treatment. Gas chromatography–mass spectrometry (GC–MS) has traditionally been used for the identification of drugs [4], providing both high selectivity and sensitivity. This comes at the expenses of fast analysis, making a real-time and therefore on-the-spot analysis impossible. Chemical test strips and ion mobility spectrometry (IMS) are much faster methods of analysis, but these have a limited selectivity [5].

Proton-Transfer-Reaction-Time of Flight-Mass-Spectrometry (PTR-ToF-MS), which relies on the use of H_3O^+ as the reagent ion, provides both a rapid detection capability and a high sensitivity

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(pptv within seconds). In addition, the soft ionisation capabilities of PTR-ToF-MS generally avoid significant fragmentation of the analytes which enables drug identification with a high level of confidence (low rate of false positives). However, relying on a nominal *m*/*z* makes unambiguous identification impossible. High mass resolution instruments provide higher confidence in assignment, but still isomeric compounds cannot be ruled out. In addition to changing operational parameters, e.g. the voltage applied to the drift tube, the recently developed Selective Reagent Ionisation (SRI) technology, [6,7] to change the reagent ion and hence alter the ion-molecule chemistry in the drift tube of a PTR-ToF-MS, has significantly increased the instrument's selectivity, making it a multidimensional technique [8]. Given that we have used SRI in this study, we will not refer to the instrument as PTR-ToF-MS, but as a Selective Reagent Ionisation-Time of Flight-Mass Spectrometry (SRI-ToF-MS) instrument to reflect this multidimensional use.

Previous studies have illustrated the applicability of SRI-ToF-MS to the detection of several illicit and controlled prescription drugs [9] and numerous other threat substances, such as explosives [10–12], chemical warfare agent simulants and toxic industrial compounds [13–15]. In addition, it has been shown that for some explosives, selectivity can be enhanced by changing the voltage applied to the drift tube (e.g. with the use of H_3O^+ as the reagent ion, by increasing reduced electric field strengths E/N – the ratio of the electric field, E, to the buffer gas number density, N, in the drift tube – the protonated parent molecule signals of TNT and TNB are increased) [12].

In this paper a detailed study of the principle product ions observed following reactions of H_3O^+, NO^+, $O_2{}^+$ and Kr^+ with a number of new psychoactive substances, namely 4-fluoroamphetamine, methiopropamine, ethcathinone, 4-methylethcathinone, N-ethylbuphedrone, ethylphenidate, 5-MeO-DALT, dimethocaine, 5-(2-aminopropyl)benzofuran and nitracaine (for structural information see Fig. 1) is reported. In particular, the effects of E/N on the fragmentation pathways are also discussed in detail. These datasets, which provide information on the exact *m*/*z* and E/N dependence for all abundant fragments and with all four reagent ions, respectively, should help in the development of a highly selective analytical technique for drug detection based on SRI-ToF-MS suitable for real world scenarios.

2. Experimental

All new psychoactive substance samples were analysed using a PTR-TOF 8000 (IONICON Analytik GmbH, Austria) equipped with a SRI capability, thus allowing a change in the reagent ion used for chemical ionisation from H_3O^+ to $O_2{}^+$, NO^+ or Kr^+. The reagent ions and the resulting product ions are separated and detected using a ToF mass analyser. PTR-ToF-MS and SRI have both been described in detail in previous publications [6,7,16,17] and therefore they will only be briefly discussed here.

For the production of H_3O^+ ions water vapour from a reservoir of pure water enters a hollow cathode discharge source. Following ionisation and a series of ion-molecule reactions the resulting H_3O^+ ions are directed into the drift tube by an applied voltage gradient. Within the drift tube proton transfer reactions will take place only with those chemical species (M) that have a proton affinity (PA) greater than that of water ($PA(H_2O) = 691\ \mathrm{kJ\,mol^{-1}}$) [18]. This could either be via non-dissociative proton transfer:

$$H_3O + M \rightarrow MH^+ + H_2O \qquad (1)$$

and/or via dissociative proton transfer:

$$H_3O^+ + M \rightarrow [M-A]H^+ + A + H_2O \qquad (2)$$

where A represents an elimination of a molecule from the transient protonated parent molecule.

For the production of $O_2{}^+$, NO^+ and Kr^+, water vapour is replaced by oxygen, an oxygen/nitrogen mix and krypton, respectively. If exothermic, the reactions with NO^+, $O_2{}^+$ and Kr^+ may proceed via charge transfer, which may also be either non-dissociative:

$$X^+ + M \rightarrow M^+ + X \qquad (3)$$

where X^+ represents the reagent ion, and/or dissociative:

$$X^+ + M \rightarrow [M-B]^+ + B + X \qquad (4)$$

resulting in the elimination of B from the parent ion. NO^+ has the lowest recombination energy (RE) of these three reagent ions (9.3 eV) and therefore may only charge transfer to neutral species whose ionisation energies (IE) are less than 9.3 eV. However, reaction of NO^+ and a molecule may also take place via a chemical reaction, for example hydride abstraction:

$$NO^+ + M \rightarrow [M-H]^+ + HNO \qquad (5)$$

Reaction with NO^+ may result in an adduct ion being formed:

$$NO^+ + M + C \rightarrow MNO^+ + C \qquad (6)$$

where C represents a third body (the buffer gas) that is required to remove some of the energy resulting from the association, without which the adduct would dissociate rapidly.

The E/N value used can be rapidly adjusted by changing the voltage applied across the drift tube; this enables the investigation of fragmentation pathways potentially offering a more selective method for compound identification. In the reported experiments the E/N value was varied between 85 and 225 Td ($1\ \mathrm{Td} = 10^{-21}\ \mathrm{V\,m^2}$) when H_3O^+, NO^+ and $O_2{}^+$ were used as reagent ions and between 45 and 115 Td for the investigations using Kr^+. The 10 new psychoactive substances studied, legal in most European countries at the time of purchase, were obtained from various online vendors. These new psychoactive substances studied were 4-fluoroamphetamine, methiopropamine, ethcathinone, 4-methylethcathinone, N-ethylbuphedrone, ethylphenidate, 5-MeO-DALT, dimethocaine, 5-(2-aminopropyl)benzofuran and nitracaine. Most can be classified as cathinones or piperazines, which include a large list of analogues of amphetamines, with psychoactive and stimulant effects [19,20]. Most of the chemicals were supplied in powder (or crystal) form. However, two were supplied in tablet form (4-fluoroamphetamine and ethcathinone). Therefore, before any measurements were taken these two compounds were first crushed into a fine powder. This ensured that all samples were of comparable surface area. All of the supplied chemicals were used with no purification. In addition to the detection of the advertised new psychoactive substance analysis with SRI-ToF-MS enables the detection of most solvents, synthetic reagents and intermediates, but not "extenders" (usually low cost inorganics such as sodium bicarbonate), however due to low costs of production and tough competition, with rankings in online forums, the use of these "extenders" is less likely in new psychoactive substances than in illegal drugs.

The following procedure was adopted for the dynamic headspace sampling of all 10 chemicals with H_3O^+, NO^+ and $O_2{}^+$ as the reagent ions. A few mg of the drug were added to a glass vial, the vial was then sealed with a septum. An inlet and an outlet line (1/16th inch PEEK, internal diameter 1 mm, VICI AG International) were inserted through the septum to allow for dynamic headspace sampling. The inlet line was connected to a charcoal filter so that purified laboratory air entered the vials. The outlet line was directly connected to the heated sampling line of the SRI-ToF-MS instrument. Samples were heated to a temperature between 60 °C and 100 °C and the sampling line and drift tube were maintained at a temperature of 110 °C in order to minimise adsorption of the analytes onto the surface and memory effects.