Supporting Information for Non-Contact Vapor Detection of Illicit Drugs via Atmospheric Flow Tube-Mass Spectrometry

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Abstract:

The real-time, non-contact detection of illicit drugs is a desirable analytical goal to inhibit the spread of illicit compounds, but conventional mass spectrometry approaches have not had adequate sensitivity for such ambient vapor measurements. However, the introduction of atmospheric flow tube-mass spectrometry (AFT-MS), which has been demonstrated to detect analytes at low parts-per-quadrillion levels previously for explosives and organophosphorus compounds, lends the potential for non-contact drug detection. Figures that elaborate on these capabilities are contained within this supporting information. Thermal desorption of low- to sub-picogram quantities of cocaine, methamphetamine, and fentanyl for AFT-MS analysis of protonated drug monomers have produced limits of detection (LODs) on the order of 10-100 femtograms. The same mode of analysis resulted in an LOD of 1.6 pg for heroin. However, the analyte selectivity can be enhanced through introduction of specific organophosphorus dopant species that can form proton-bound heterodimers with target drugs according to their respective ion chemistries. With respect to heroin, AFT-MS analysis of the heroin-dopant heterodimer resulted in an LOD of 300 fg, which is approximately one order of magnitude lower than analysis of the protonated heroin monomer. This approach has the potential to be applied to other drug species, but cocaine was found to form only a small quantity of proton-bound dimers with organophosphorus compounds. This poor dimer formation by cocaine was thought to be due to internal hydrogen bonding within the cocaine molecule upon protonation. In addition to figures pertaining to trace detection of the four drugs, this supporting information contains a simple depiction of the six-membered ring created by intramolecular hydrogen bonding in protonated cocaine, structures of cocaine analogs used for survival yield analysis, and the survival yield results in both a figure and descriptive text.

Key words: methamphetamine, cocaine, heroin, fentanyl, atmospheric flow tube-mass spectrometry, trace detection, gas-phase ion chemistry, vapor detection

Figure S-1.) Intramolecular interaction between the tertiary amine when protonated and carbonyl oxygen of cocaine's methyl ester yields a stabilized 6-membered ring. Because of the hydrogen bonding interaction that spreads the charge within the molecule, cocaine is less likely to form a proton-bond heterodimer with tributyl phosphate than amines that do not have an intramolecular hydrogen bond. Lone pair electrons in the structure are labeled as Lp.

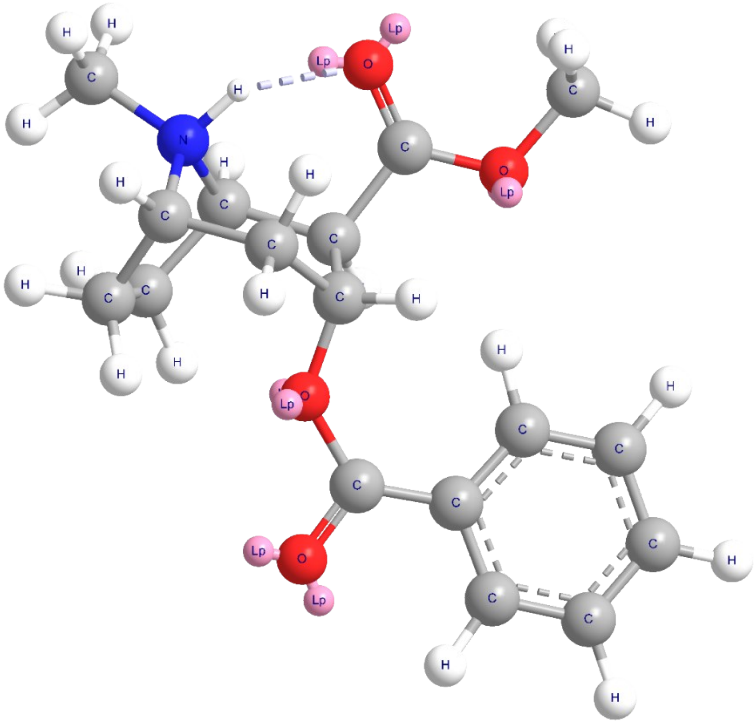


Figure S-2.) Structures of the cocaine surrogates used for survival yield analysis (tropacocaine, tropane, and tetracaine) are shown in addition to cocaine itself. The tertiary nitrogen atoms that are likely sites of protonation are depicted in blue, while the oxygen atoms in red are those with potential for intramolecular interaction with the protonated nitrogen atoms.

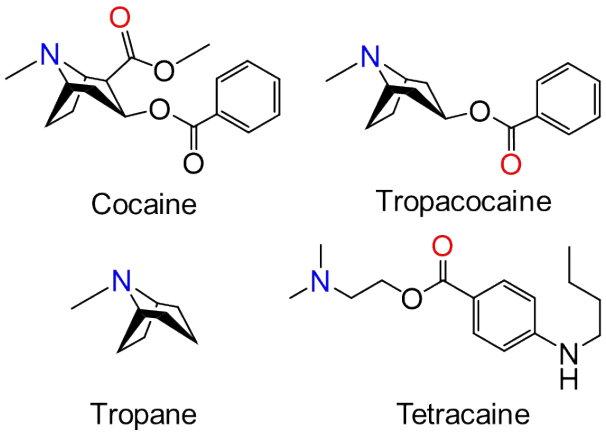


Figure S-3.) Survival yield analysis of tropane, tropacocaine, and tetracaine proton-bound dimers with TBP indicates that the relative TBP dimer interaction strengths observed were tropacocaine > tropane > tetracaine. Error bars corresponding to ± one standard deviation have been included on all data points.

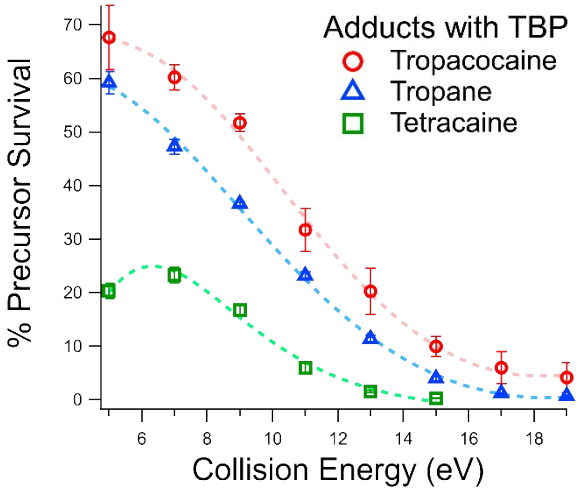


Figure S-4.) MRM signal traces obtained for 1, 5, 10, and 25 pg methamphetamine samples. Note that for each sample mass deposited, a partial evaporation of the analyte was observed following the closure of the desorption chamber. This resulted in an immediate response, which corresponds to the first peak indicated for each sample mass (labeled as sample chamber closed). This was followed by a 2 min drying time and then thermal desorption of the remaining methamphetamine to produce the second peak per sample (labeled as desorption).

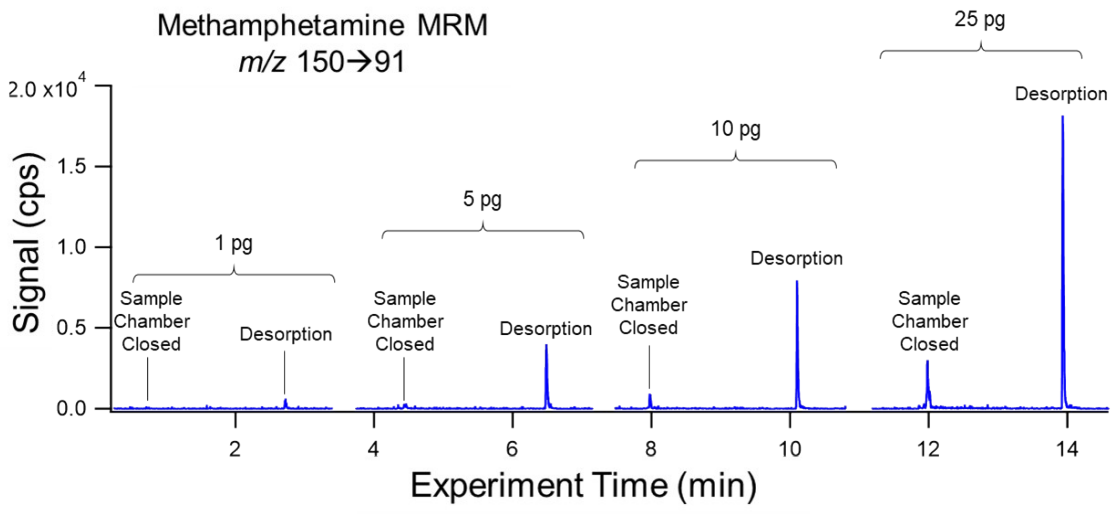


Figure S-5.) Calibration curve trendlines for MRM analysis of **a)** methamphetamine, **b)** cocaine, and **c)** heroin. All points have error bars corresponding to ± one standard deviation.

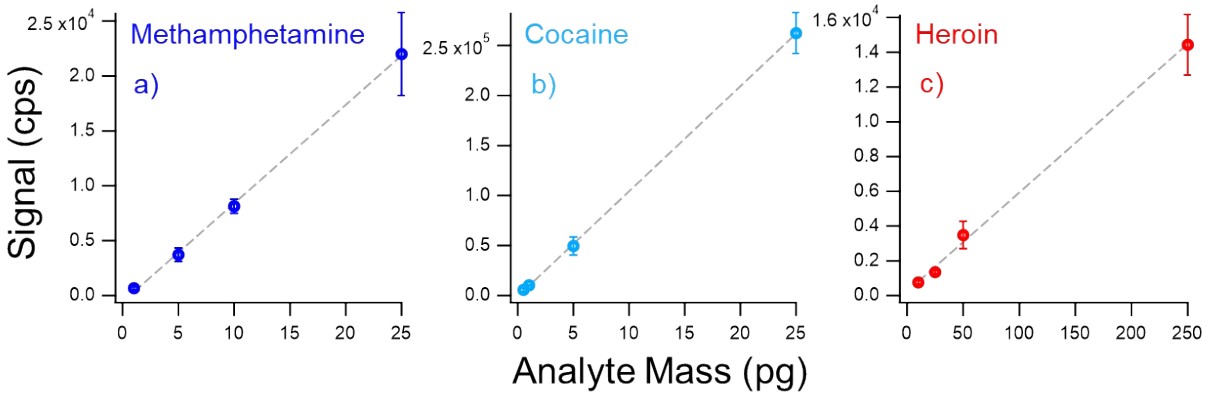


Figure S-6.) Shown in this figure are calibration curves demonstrating four different modes of heroin analysis examined, including **a)** SIM of the protonated monomer, **b)** MRM of the protonated monomer, **c)** SIM of the heroin-TBP proton-bound dimer, and **d)** MRM of the heroin-TBP proton-bound dimer. Note the presence of elevated baselines from blank desorptions in both SIM traces **(a, c)**.

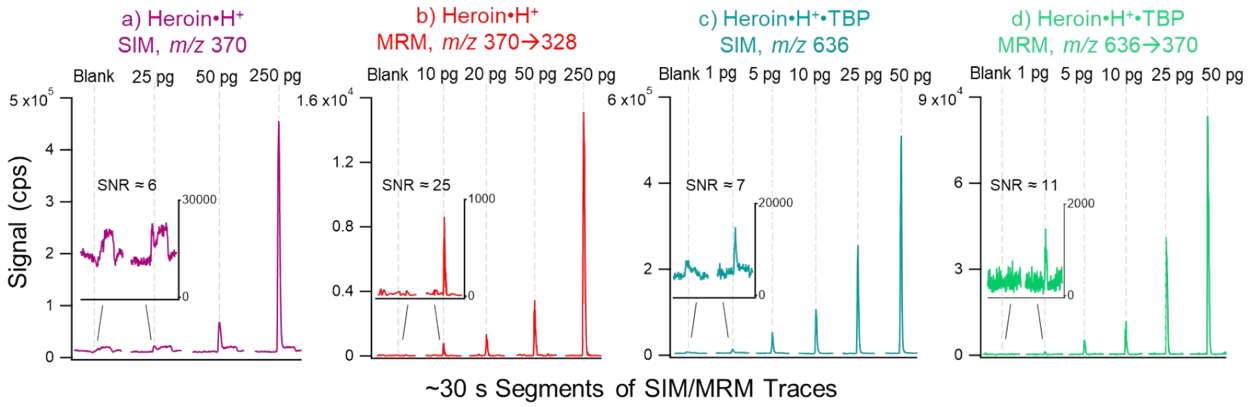
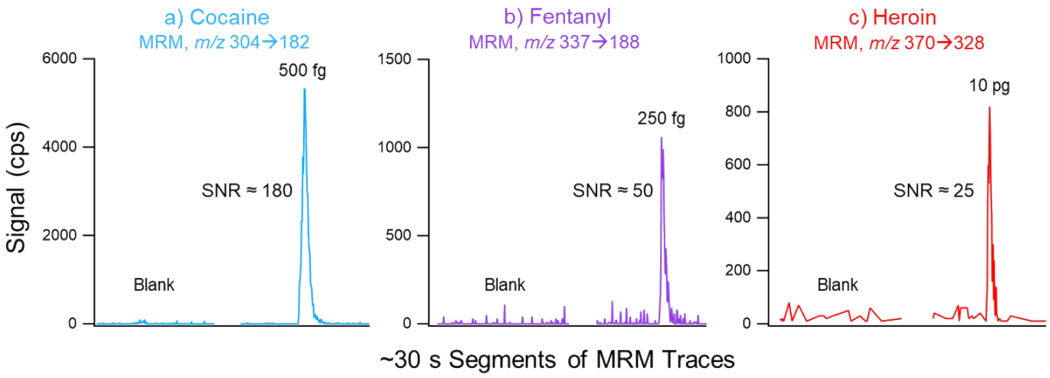


Figure S-7.) Segments of MRM traces of the blank desorptions and lowest sample quantities analyzed for **a)** cocaine, **b)** fentanyl, and **c)** heroin. These expanded plots convey noise levels in comparison to peaks and are supplementary to the zoomed-in sections in Figure 5 from the main article.



Survival-Yield Experiment with Cocaine Analogs

Internal bridging of a protonated amine functional group with a nearby oxygen may reduce the ability of molecules exhibiting such bridging to form adducts with an external dopant like TBP. Unlike with methamphetamine and heroin, only a small quantity of cocaine was observed as an adduct with TBP. Although the low dimer response is not helpful for trace quantitative analysis, there is still value in forming the dimer to confirm the presence of cocaine in a lower background region of the mass spectrum. Given the visible signal enhancement conferred by TBP dimerization with methamphetamine and heroin, there is merit to exploring potential reasons why this improvement may not occur with cocaine. A close inspection of the chemical structure reveals, that upon protonation of the amine, an internal six-membered hydrogen bonded ring can form with the carbonyl within the cocaine molecule. A rough representation of the ring structure can be found in Figure S-1 (Supporting Information). This intramolecular hydrogen bonding within cocaine is a reasonably well-documented structure both from theoretical gas- and liquid-phase structures[1-6] in addition to x-ray crystallographic data of a cocaine salt.[7] Because protonated cocaine can readily create this intramolecular interaction, any additional hydrogen bonds forming with the protonated amine or with the carbonyl oxygen will be weaker than if the intramolecular hydrogen bonding were not occurring. Publications by Meot-Ner et al.[8-11] and Ibrahim et al.[12] among others have documented how charge is shared across more interactions and subsequently weakened as proton-bound adducts have subsequent additions of molecules to increase the overall size of an adduct. Since protonated cocaine in the gas phase has a high probability of forming an intramolecular six-membered ring with the hydrogen bonded proton, the interaction of protonated cocaine with TBP will be consistently weaker than TBP's interaction with other drug species that do not form intramolecular hydrogen bonds.

To explore the intramolecular bonding further, the relative proton-bound dimer strength between TBP and the three cocaine analogs (tropacocaine, tropane, and tetracaine; see Figure S-2, Supporting Information), was qualitatively assessed. Survival yield experiments were performed on the three target adducts using a procedure similar to that described by Morrison et al.[13,14] for organophosphorus compound adducts with amines. In brief, the target compounds to be adducted with TBP were introduced to the AFT-MS system as headspace vapor over vials of dopant. Collision-induced dissociation was performed on the TBP-analyte proton-bound dimer precursor ions covering collision voltages from 5 eV up to 15 eV (tetracaine) and 19 eV (tropacocaine and tropane) in 2 eV increments. Low collision energies were used specifically with the intention to dissociate the adducts into component protonated monomers, but not to produce fragmentation of covalent bonds. At these low collision energies, the intact molecular components were produced without further fragmentation. A minimum of 3 replicates of 2-minute, multi-channel averaged dissociation experiments were performed for each voltage. By performing the tandem MS experiments at increasing collision voltages, the precursor adducts are effectively titrated with greater amounts of energy and the relative amount of precursor that survives at a given voltage is indicative of the comparative interaction strength among the three proton-bound dimers. The survival yield (%SY) is calculated as the percent precursor ion abundance remaining after dissociation relative to the total ion current measured.[14,15] The %SY value at a given collision energy conveys the relative stability of each TBP-analyte heterodimer under those dissociation conditions. A greater %SY for one adduct over another indicates that the interaction between the dimer partners of the first adduct is stronger than the dimer interaction within the other adduct.

Tropacocaine, tropane, and tetracaine were used as proxies to explore the stability of TBP dimers. These species are similar in structure to cocaine, both with and without the influence of an internal hydrogen bond. Tropacocaine is the most like cocaine with respect to overall structure; the tropacocaine molecule results from simply removing the methyl ester moiety, thereby assessing how well cocaine would dimerize with TBP in the absence of forming the stable, six-membered intramolecular hydrogen bond. The tertiary amine and associated alkyl structures within cocaine are collectively known as a tropane group (Figure S-2, Supporting Information), so the tropane molecule examines cocaine's interaction with TBP resulting only from the tropane amine. Finally, tetracaine was included as a species that differs the most in actual structure from cocaine, but still contains a tertiary amine and carbonyl oxygen in the structure. Protonated tetracaine forms an intramolecular hydrogen bond, although in the form of a seven-membered ring that is slightly less stable than the six-membered ring formed within cocaine.[16]

The TBP-amine adducts for tropacocaine, tropane, and tetracaine were subject to increasingly higher collision voltages in the tandem mass spectrometry experiments until the precursor ion species were no longer visible (Figure S-3, Supporting Information). Figure S-3 illustrates the stability trends of the dimers with TBP and how they behave based upon the presence or absence of intramolecular hydrogen bonding. Both tropacocaine and tropane are unable to form intramolecular hydrogen bonds, and these two species yielded similar trends in precursor survival. Tropacocaine and tropane both exhibited >50% precursor ion survival at the lowest collision energy examined, 5 eV, and neither species fell below 10% survival yield until subjected to voltages in excess of 13 eV. In contrast, the dimer between tetracaine and TBP appeared to be more fragile than the other two dimers. At a collision energy of 5 eV, the tetracaine-TBP dimer produced <25% survival of the precursor ion, and no survival yield experiments were performed at voltages beyond 15 eV for the tetracaine-TBP dimer because the remaining precursor abundance had fallen below 1%. The cocaine dimer with TBP itself was not assessed by survival yield analysis because the adduct was so fragile that no remaining precursor ion was visible at the 5-eV minimum collision energy.

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