REPORT DOCUMENTATION PAGE

Form Approved OMB NO. 0704-0188

1. REPORT DATE (DD-MM-YYYY)	2. REPORT TYPE	3. DATES COVERED (From - To)
11-06-2021	Final Report	15-Sep-2015 - 14-Oct-2020

4. TITLE AND SUBTITLE
Final Report: Kinetics of High Pressure Ionization Mechanisms to Enable Real-Time Ultra-Trace Detection of Organics from Environmental Matrices

5a. CONTRACT NUMBER
W911NF-15-1-0619

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER
611102

6. AUTHORS

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAMES AND ADDRESSES
Washington State University
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Pullman, WA 99164 -3140

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS (ES)
U.S. Army Research Office
P.O. Box 12211
Research Triangle Park, NC 27709-2211

10. SPONSOR/MONITOR'S ACRONYM(S)
ARO

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
68027-CH.28

12. DISTRIBUTION AVAILIBILITY STATEMENT
Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES
The views, opinions and/or findings contained in this report are those of the author(s) and should not contrued as an official Department of the Army position, policy or decision, unless so designated by other documentation.

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	15. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Brian Clowers
UU	UU	UU	UU		19b. TELEPHONE NUMBER: 509-335-4300

RPPR Final Report
as of 14-Jun-2021

Agency Code: 21XD

Proposal Number: 68027CH **Agreement Number: W911NF-15-1-0619**
INVESTIGATOR(S):

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Principal: Y

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Address: 423 Neill Hall, Pullman, WA 991643140
Country: USA
DUNS Number: 041485301 EIN: 916001108
Report Date: 14-Jan-2021 Date Received: 11-Jun-2021
Final Report for Period Beginning 15-Sep-2015 and Ending 14-Oct-2020
Title: Kinetics of High Pressure Ionization Mechanisms to Enable Real-Time Ultra-Trace Detection of Organics from Environmental Matrices
Begin Performance Period: 15-Sep-2015 **End Performance Period:** 14-Oct-2020
Report Term: 0-Other
Submitted By: Ph.D. Brian Clowers Email: brian.clowers@wsu.edu
Phone: (509) 335-4300
Distribution Statement: 1-Approved for public release; distribution is unlimited.

STEM Degrees: 3 **STEM Participants:** 2

Major Goals: To minimize the complexities of field-based sampling and realize extremely low levels of sensitivity, this project aims to characterize the kinetic routes of high-pressure ionization mechanisms that enable ultra-trace level detection schemes using a kinetic reaction atmospheric flow tube (KRAFT). When combined with mass spectrometry (MS) this adaptive and selective ionization system will provide forensic investigators with a tractable, non-destructive, real-time method to quantify chemical warfare agents (CWAs), toxic industrial compounds (TICs), and their degradation products. However, until such goals are realized a fundamental understanding of ion clustering kinetics are required. Using a combination of rapid gas-phase ion separations (i.e. ion mobility spectrometry (IMS)) and MS the proposed research will probe the central hypothesis that thermodynamics measurements can aid in the design of selective gas-phase reactions that produce stable ion clusters that are highly amenable to detection using MS. Identifying the conditions that produce selective ion clustering, not simply charge transfer, will directly aid the environmental forensics community while establishing the framework for highly adaptable and selective ionization schemes. The fundamental principles and technique developed under this research effort will be pursued across three specific aims.

Specific Aim 1: High Pressure Thermodynamic Characterization of Gas-Phase Clusters of Common CWA and TIC Degradation Products. Building upon initial observations in the PI's laboratory the kinetics of cluster formation for select CWAs along with their degradation products will be determined using an innovative KRAFT-MS system.

Specific Aim 2: Design of Selective Adducts for Gas-phase Complexation. In order to extend the KRAFT-MS approach to a suite of TICs and toxic industrial materials (TIMs) a logical series of competition experiments will be executed. This aim will leverage the results from previous project stages, employ computational chemistry techniques, and test the hypothesis that common functional groups found within target analytes may aid in the selection of ideal clustering agents.

Specific Aim 3: Assessment of Detection Limits for Gas-Phase Ion Pairing Reagents from Complex Matrices. Serial dilution experiments will be performed to assess the detection limits, signal-to-noise ratio and required analysis time for each of the target chemicals using the range of selective adducts outlined in Aims 1 and 2. An additional goal of this Aim is to explore the simultaneous use of multiple gas-phase ion-pairing reagents for different chemical classes.

At the completion of these studies, it is our expectation that we will have established the chemical foundations for a

new class of analytical techniques aimed at the real-time detection of analytes relevant to the mission of the Army Research Office (e.g. CWA degradation products, decontamination solvents, and common ground water contaminants). Additional benefits of this approach include non-contact sampling and highly competitive detection limits (< 1 ppm by volume in the gas-phase) using an innovative high-pressure ionization technique. Though initially tailored to CWA agents and their degradation products, the underlying approach to establish the gas-phase properties of high-pressure ion clustering can be extended to other organics in the environment that are of interest. Real-time, highly sensitive techniques are essential to rapidly evaluated the complex chemistry occurring in complex environmental matrices.

In addition to the education of students in the fields of analytical and physical chemistry, the broader reaching outcomes include peer-reviewed publications detailing the thermochemical clustering information of target analytes in the gas-phase which is largely absent from existing literature. Additionally, it is envisioned that the KRAFT-MS approach to vapor detection may find utility in other disciplines such as biology and synthetic chemistry.

Accomplishments: Please see the attached Final Report

Training Opportunities: The funding supplied by ARO under this effort supported 3 graduate students in chemistry at from Washington State University:

Pearl Kwantwi-Barima, Ph.D. – Clowers Group – Graduation Date: 2020
Kelsey Morrison, Ph.D. – Clowers Group – Graduation Date: May, 2019
Peyton Nosbusch, M.S. – Clowers Group – Graduation Date: May, 2018

Kelsey Morrison completed an exemplary graduate school career in May 2019 and is currently employed in the National Security Directory at Pacific Northwest National Laboratory focusing on trace threat detection. Though a different candidate was selected for the award, Kelsey was also a finalist for the Linus Pauling Distinguished Post-Doctoral Fellowship. This award process was extremely rigorous and required multiple rounds of interviews and presentations. It is also worthy to note that Dr. Morrison published 9 first-author manuscripts as a graduate student and is poised to realize a total of 13 publications during her time at WSU. Support from ARO was integral in training and success, ultimately leading to the start of a career in national-security and analytical chemistry.

Pearl Kwantwi-Barima completed her degree focusing on the core fundamentals of gas-phase clustering interactions. In addition to making key instrumental improvements, Pearl has expanded the range of compounds explored using the newly developed clustering model (initially reported in Year 2) to a range of other compounds. Dr. Kwantwi-Barima published 5 first-author manuscripts with support from ARO and is currently a post-doctoral researcher within the National Laboratory complex.

Results Dissemination: See attached Final Report

Honors and Awards: The KRAFT-MS technology (though termed differently for the award) was awarded the R&D 100 Award in 2019 (https://www.pnnl.gov/about/rd-100-awards).

Protocol Activity Status:

Technology Transfer: Nothing to Report

PARTICIPANTS:

Participant Type: PD/PI
Participant: Brian H Clowers Ph.D.
Person Months Worked: 1.00 **Funding Support:**
Project Contribution:
National Academy Member: N

RPPR Final Report
as of 14-Jun-2021

ARTICLES:

Publication Type: Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
Journal: Analytical Chemistry
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.analchem.7b03518
Volume: Issue: First Page #:
Date Submitted: 8/29/18 12:00AM Date Published:
Publication Location: Washington, D.C.
Article Title: Tuning Mobility Separation Factors of Chemical Warfare Agent Degradation Products via Selective Ion-Neutral Clustering
Authors: Pearl Kwantwi-Barima, Hui Ouyang, Christopher J. Hogan Jr., Brian H. Clowers
Keywords: Ion Mobility, Ion-Neutral Clustering, Thermodynamics, Chemical Warfare Agents
Abstract: Combining experimental data with computational modeling, we illustrate the capacity of selective gas-phase interactions using neutral gas vapors to yield an additional dimension of gas-phase ion mobility separation. Not only are the mobility shifts as a function of neutral gas vapor concentration reproducible, but also the selective alteration of mobility separation factors is closely linked to existing chemical functional groups. Such information may prove advantageous in elucidating chemical class and resolving interferences. Using a set of chemical warfare agent simulants with nominally the same reduced mobility values as a test case, we illustrate the ability of the drift-gas doping approach to achieve separation of these analytes.
Distribution Statement: 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support: **Y**

Publication Type: Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
Journal: Talanta
Publication Identifier Type: DOI Publication Identifier: https://doi.org/10.1016/j.talanta.2018.11.115
Volume: 195 Issue: 683 First Page #:
Date Submitted: 9/1/19 12:00AM Date Published:
Publication Location: Washington, D.C.
Article Title: Ambient Vapor Sampling and Selective Cluster Formation for the Trace Detection of Tributyl Phosphate via Kinetic Reaction Atmospheric Flow Tube Mass Spectrometry
Authors: Kelsey A. Morrison, Robert G. Ewing, Brian H. Clowers
Keywords: Ambient vapor sampling; Dielectric barrier discharge ionization (DBDI); Mass spectrometry; Tributyl phosphate (TBP); Nuclear extractants; Environmental Monitoring
Abstract: Because detection of trace quantities of TBP can be indicative of a specific activity or provide insight into the degradation routes in the environment, it is of utmost importance that minute amounts of TBP can be detected in real time while also having the sampling process occur inconspicuously. Vapor detection at atmospheric pressure is one method that fits both needs, so correspondingly we present here the use of atmospheric flow tube mass spectrometry (AFT-MS) for the ambient vapor sampling of protonated TBP from headspace out of ppb-level solutions in methanol. Furthermore, we have made use of gas phase clustering reactions to enhance lower levels of TBP detection via the addition of small quantities of the dopants diethylamine (DEA) and pinacolyl methylphosphonate (PMP) in the vapor stream.
Distribution Statement: 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support: **Y**

RPPR Final Report
as of 14-Jun-2021

Publication Type: Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
Journal: Rapid Communications in Mass Spectrometry
Publication Identifier Type: DOI Publication Identifier: 10.1002/rcm.8177
Volume: 32 Issue: 16 First Page #: 1363
Date Submitted: 8/29/18 12:00AM Date Published: 8/1/18 2:00PM
Publication Location:
Article Title: Characterization of alkylphosphonic acid vapors using atmospheric flow tube-ion trap mass spectrometry
Authors: Kelsey A. Morrison, Brian H. Clowers
Keywords: Ion Chemistry, Mass Spectrometry, Trace Detection, Phosphonic Acids
Abstract: A key aspect of detecting hazardous compounds at ultra?trace levels for processing, compliance, and clean?up purposes involves developing methods that are not only sensitive, but also highly selective with minimal sampling effort. Atmospheric flow tube mass spectrometry (AFT?MS) using dielectric barrier discharge ionization has emerged as a technique that combines such features for vapor detection. AFT?MS is thus appealing for application to ambient screening for chemical warfare agents (CWAs) and their degradation products. Initial characterization of AFT?MS for CWA detection necessitates examining less harmful simulant species. A predominant hydrolysis product of most organophosphorus CWAs is methylphosphonic acid and most other hydrolysis products consist of some form of an alkylphosphonic acid. The series of phosphonic acids demonstrated consistent relative ion abundances thought to be related at least in part to the relative vapor pressures depending on their alkyl chains.
Distribution Statement: 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support: **Y**

Publication Type: Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
Journal: Journal of The American Society for Mass Spectrometry
Publication Identifier Type: DOI Publication Identifier: 10.1007/s13361-019-02202-w
Volume: 30 Issue: 7 First Page #: 1308
Date Submitted: 9/1/19 12:00AM Date Published: 4/1/19 7:00AM
Publication Location:
Article Title: Interrogating Proton Affinities of Organophosphonate Species Via Atmospheric Flow Tube Mass Spectrometry and Computational Methods
Authors: Kelsey A. Morrison, Benjamin J. Bythell, Brian H. Clowers
Keywords: Ion Mobility, Thermodynamics, Gas-Phase Clusters
Abstract: Through vapor modification of the counter-current drift gas in an atmospheric pressure drift tube ion mobility spectrometer (IMS), we demonstrate measurement of gas-phase association enthalpies and entropies for select proton-bound heterodimers formed from a phosphonic acid with 2-propanol. Previous efforts to determine gas-phase association thermodynamic properties have relied largely upon lower pressure systems and inference of the relative concentrations of m/z isolated species. In contrast, the drift tube IMS based approach developed and applied in this study leverages the explicit gas-phase equilibrium that is established within an ion mobility drift cell. The inferred enthalpies and entropies of association are based solely upon monitoring a shift in the arrival time of an ion at different temperatures (and not on the signal intensity or on external instrument drift time calibration).
Distribution Statement: 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support: **Y**

RPPR Final Report
as of 14-Jun-2021

Publication Type: Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
Journal: The Journal of Physical Chemistry A
Publication Identifier Type: DOI Publication Identifier: 10.1021/acs.jpca.8b11183
Volume: 123 Issue: 13 First Page #: 2957
Date Submitted: 9/1/19 12:00AM Date Published: 3/1/19 8:00AM
Publication Location:
Article Title: Deducing Proton-Bound Heterodimer Association Energies from Shifts in Ion Mobility Arrival Time Distributions
Authors: Pearl Kwantwi-Barima, Christopher J. Hogan, Brian H. Clowers
Keywords: Ion Mobility, Gas-Phase Clusters, Thermodynamics
Abstract: Through vapor modification of the counter-current drift gas in an atmospheric pressure drift tube ion mobility spectrometer (IMS), we demonstrate measurement of gas-phase association enthalpies and entropies for select proton-bound heterodimers formed from a phosphonic acid with 2-propanol. Previous efforts to determine gas-phase association thermodynamic properties have relied largely upon lower pressure systems and inference of the relative concentrations of m/z isolated species. In contrast, the drift tube IMS based approach developed and applied in this study leverages the explicit gas-phase equilibrium that is established within an ion mobility drift cell. The inferred enthalpies and entropies of association are based solely upon monitoring a shift in the arrival time of an ion at different temperatures (and not on the signal intensity or on external instrument drift time calibration).
Distribution Statement: 3-Distribution authorized to U.S. Government Agencies and their contractors
Acknowledged Federal Support: **Y**

CONFERENCE PAPERS:

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: International Society for Ion Mobility Spectrometry
Date Received: 25-Aug-2016 Conference Date: 28-Jul-2016 Date Published: 28-Jul-2016
Conference Location: Boston, MA
Paper Title: Open-Source, Modular Approaches for Ion Mobility Spectrometry
Authors: Brian H. Clowers, Gordon A. Anderson, Kelsey Morrison, Peyton Nosbusch, Austen L. Davis
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: Washington State University Showcase for Undergraduate Research and Creative Activities
Date Received: 31-Aug-2017 Conference Date: 29-Mar-2016 Date Published: 29-Aug-2016
Conference Location: Pullman, WA
Paper Title: Rapid Ambient Pressure Detection of Nuclear Extractants and Chemical Warfare Agent Simulants via Kinetic Reaction Atmospheric Flow Tube-Mass Spectrometry
Authors: John T. Rodgers, Kelsey A. Morrison, Brian H. Clowers
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: The Great Scientific Exchange (SciX) 2016
Date Received: 31-Aug-2017 Conference Date: 16-Sep-2016 Date Published: 16-Sep-2016
Conference Location: Minneapolis, MN
Paper Title: Modification of Drift Gas Composition to Isolate Chemical Classes using Drift-Tube Ion Mobility Mass Spectrometry. Brian H. Clowers
Authors: Clowers, B.H., Zhihao, Y., Kwantwi-Barima, P.
Acknowledged Federal Support: **Y**

RPPR Final Report
as of 14-Jun-2021

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: Annual Meeting for the American Society for Mass Spectrometry
Date Received: 31-Aug-2017 Conference Date: 04-Jun-2017 Date Published: 04-Jun-2017
Conference Location: Indianapolis, IN
Paper Title: Selective Ion-Neutral Clustering to Enhance Ion Mobility Separation Factors
Authors: Pearl Kwantwi-Barima, Brian H. Clowers
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: Gas-Phase Ion Chemistry, Gordon Conference 2017
Date Received: 31-Aug-2017 Conference Date: 08-Feb-2017 Date Published: 08-Feb-2017
Conference Location: Ventura, CA
Paper Title: Tuning Mobility Separation Factors via Selective Ion-Neutral Clustering
Authors: rian H. Clowers, Pearl Kwantwi-Barima
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: The Great Scientific Exchange (SciX) 2017
Date Received: 29-Aug-2018 Conference Date: 09-Oct-2017 Date Published: 13-Oct-2017
Conference Location: Reno, NV
Paper Title: Tuning Mobility Separation Factors for Metabolomics via Selective Ion-Neutral Clustering
Authors: Brian Clowers
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: American Socity for Mass Spectrometry
Date Received: 30-Aug-2018 Conference Date: 04-Jun-2018 Date Published: 08-Jun-2018
Conference Location: San Diego, CA
Paper Title: Deducing Association Energies from Shifts in Arrival Time Distributions: Impacts of Selective Gas-Phase Ion-Vapor Clustering
Authors: Pearl Kwantwi Barima, Christopher J. Hogan, Brian H. Clowers
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: Northwest Regional Meeting (ACS)
Date Received: 30-Aug-2018 Conference Date: 25-Jun-2018 Date Published: 29-Jun-2018
Conference Location: Richland, WA
Paper Title: Selective Gas-Phase Ion-Vapor Clustering to Enhance Ion Mobility Separation Factors: Deducing Association Energies
Authors: Pearl Kwantwi -Barima, Christopher J. Hogan, Brian H. Clowers
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: Northwest Regional Meeting (ACS)
Date Received: 30-Aug-2018 Conference Date: 19-Jun-2018 Date Published: 29-Jun-2018
Conference Location: Richland, WA
Paper Title: Chemical Warfare Agent Simulant Speciation and Detection via Atmospheric Flow Tube-Mass Spectrometry
Authors: Kelsey A. Morrison, Brian H. Clowers
Acknowledged Federal Support: **Y**

RPPR Final Report
as of 14-Jun-2021

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: International Conference on Ion Mobility Spectrometry
Date Received: 30-Aug-2018 Conference Date: 23-Jul-2018 Date Published: 27-Jul-2018
Conference Location: Calgary, ON
Paper Title: Interrogating the Extensive Gas-Phase Clustering of Organophosphonate Species via Atmospheric Flow Tube-Mass Spectrometry
Authors: Kesley A. Morrison, Brian H. Clowers
Acknowledged Federal Support: **Y**

Partners

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I certify that the information in the report is complete and accurate:
Signature: Brian H. Clowers
Signature Date: 6/11/21 1:01PM

Final Technical Report

Kinetics of High-Pressure Ionization Mechanisms to Enable Real-Time Ultra-Trace Detection of Organics from Environmental Matrices

Prepared for:

Army Research Office
Frontier 800
800 Park Offices Drive
Research Triangle Park, NC 27709

Award Number:

W911NF1510619

For the Period:

2015-2020

Submitted by:

Brian H. Clowers, Ph.D., Principal Investigator

Washington State University
Department of Chemistry
Pullman, WA 99164

Abstract: To minimize the complexities of field-based sampling and realize extremely low levels of detection, this project aims to characterize the kinetic routes of high-pressure ionization mechanisms that enable ultra-trace level detection schemes using a kinetic reaction atmospheric flow tube (KRAFT). When combined with mass spectrometry (MS) this adaptive and selective ionization system provides forensic investigators with a tractable, non-destructive, real-time method to quantify chemical warfare agents (CWAs), toxic industrial compounds (TICs), and their degradation products. Adapting the outlined approach to new applications is highly dependent upon a clear understanding of the clustering thermodynamics of the target analyte with the associated reactant ions. Using a combination of rapid gas-phase ion separations (i.e. ion mobility spectrometry (IMS)) and MS the proposed research demonstrated how the selective gas-phase reactions that produce stable ion clusters can enhance detection limits across analyte classes (e.g. CWAs, explosives, and narcotics). Identifying the conditions that produce selective ion clustering, not simply charge transfer, proved essential in maximizing the probability of detection and signal to noise ratio. Across the experimental effort new experimental techniques and approaches were developed that assess thermodynamic stability and inform future efforts to enhance detection metrics for a variety of analytes in the vapor phase. In addition to the scientific contributions and peer-reviewed publications this project supported the education and training of 3 graduate students leading to a total of 3 degrees (2 Ph.D. and 1 M.S.).

Introduction and Background

To minimize the complexities of field-based sampling and realize extremely low levels of sensitivity, this project aims to characterize the kinetic routes of high-pressure ionization mechanisms that enable ultra-trace level detection schemes using a kinetic reaction atmospheric flow tube (KRAFT). When combined with mass spectrometry (MS) this adaptive and selective ionization system will provide forensic investigators with a tractable, non-destructive, real-time method to quantify chemical warfare agents (CWAs), toxic industrial compounds (TICs), and their degradation products. However, until such goals are realized a fundamental understanding of ion clustering kinetics are required. Using a combination of rapid gas-phase ion separations (i.e. ion mobility spectrometry (IMS)) and MS, the proposed research probed the central hypothesis that thermodynamics measurements can aid in the design of selective gas-phase reactions that produce stable ion clusters that are highly amenable to detection using MS. By identifying the conditions that produce selective clustering between the target analyte and reactant ions, the outlined research accomplishments provide the environmental forensics community with a new set of highly adaptable and selective ionization schemes. The outlined research tools, strategies and techniques were applied to a range of analytes including, trace levels of phosphonic acids, thiodiglycol, explosives, and narcotics. These research successes were achieved by focusing on 3 fundamental, interrelated Specific Aims.

Specific Aim 1: High Pressure Thermodynamic Characterization of Gas-Phase Clusters of Common Chemical Warfare Agent Simulants and Degradation Products of Toxic Industrial Compounds. When formed, the selective clustering between target analytes and reactant ions establish conditions that minimize chemical background and maximize confidence during analysis. Figure 1 illustrates the signal-to-noise (SNR) benefits afforded by selective clustering when probing tributyl phosphate (TBP) vapor.

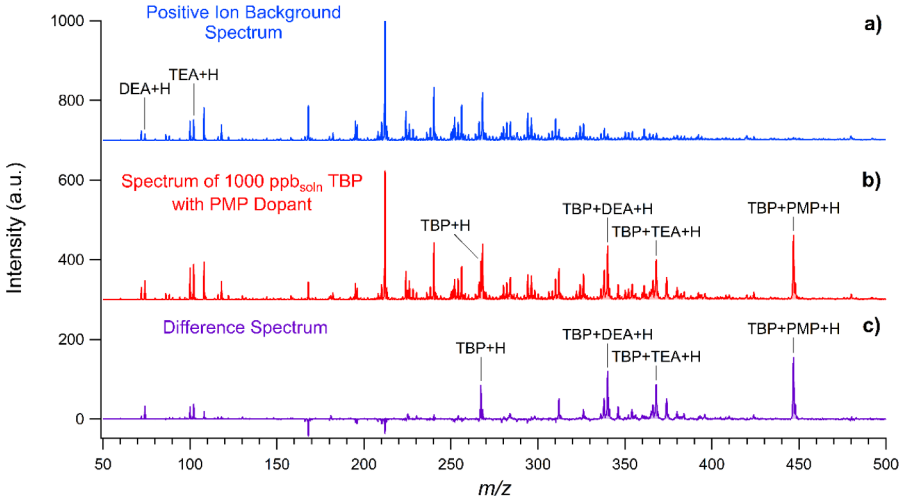

Figure 1. *a) Background mass spectrum monitoring positive ions obtained with AFT-MS for background room air, without TBP solution or dopant slides held at flow tube inlet. B) Spectrum obtained from sampling headspace over 1000 ppb$_{soln}$ TBP solution and PMP dopant slide in place. c) Difference spectrum obtained by subtracting background spectrum in (a) from TBP sample spectrum in (b).*

Careful investigation of the thermodynamic characteristics of the selective ion-neutral clusters with assistance from historical efforts, illustrated that the strength of the ion neutral cluster, and consequently its probability of detection, is dependent upon the relative thermodynamic stability of the system (i.e. the relative charge affinity between the two molecules).

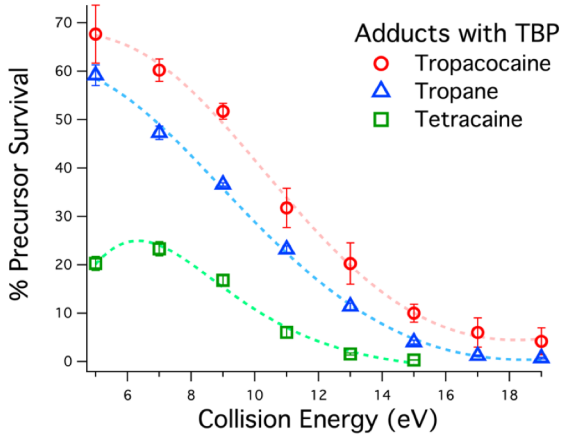

Figure 2. Survival yield analysis of TBP clusters. The diminished stability of tetracaine is attributed to the extended distance between the amine and carbonyl groups within this molecule and the role this distance plays on the stability of the gas-phase complex.

Specific Aim 2: Design of Selective Adducts for Gas-phase Complexation. In order to extend the KRAFT-MS approach to a suite of TICs and toxic industrial materials (TIMs) a logical series of competition experiments were conducted. Figure 2 illustrates the results of one such experiment evaluating the use of TBP as a clustering reagent for select opioid analogues. Slower rates of decline demonstrate higher degrees of stability and computational evaluation of the clustering participants provides insights into the data-driven selection of clustering reagents for a particular application.

Specific Aim 3: Assessment of Detection Limits for Gas-Phase Ion Pairing Reagents from Complex Matrices. Serial dilution experiments will be performed to assess the detection limits, signal-to-noise ratio and required analysis time for each of the target chemicals using the range of selective adducts outlined in Aims 1 and 2. An additional goal of this Aim is to explore the simultaneous use of multiple gas-phase ion-pairing reagents for different chemical classes.

While the full range of relevant trace detection efforts has yet to be explored using KRAFT, the outlined research success highlight the capacity of the system to realize trace detection of vapor analytes in real-time. Though initially tailored to CWA agents and their degradation products, the underlying approach to establish the gas-phase properties of high-pressure ion clustering was demonstrated across analyte classes including sulfur-containing CWA simulants, narcotics, and explosives. In addition to the education of students in the fields of analytical and physical chemistry, the broader reaching outcomes included 11 peer-reviewed publications detailing the thermochemical clustering information of target analytes in the gas-phase which is largely absent from existing literature.

Kinetic Reaction Atmospheric Flow Tube Mass Spectrometry (KRAFT-MS)

The atmospheric flow tube used in these efforts is best described as a real-time mass spectrometric method that maximizes the number of ion-neutral interactions prior to detection using mass spectrometry. When ionized reagents are present the probability of forming the produce of interest is also maximized. Historically, most ion sources are located immediately in front of the mass spectrometer inlet, however, this instrumental configuration largely eliminates any reactions that do not occur within a few milliseconds. In the KRAFT-MS system reaction times extend up to 10s. It is understood that the ultimate number of ions reaching the detector using KRAFT-MS is diminished, however, the primary goal in analytical sciences to maximize SNR. In this respect, KRAFT achieves such a goal because only ions (or clusters) that remain stable through the process are detected. When conditions are established where the analyte of interest participates in the clustering, a highly sensitive tool emerges.

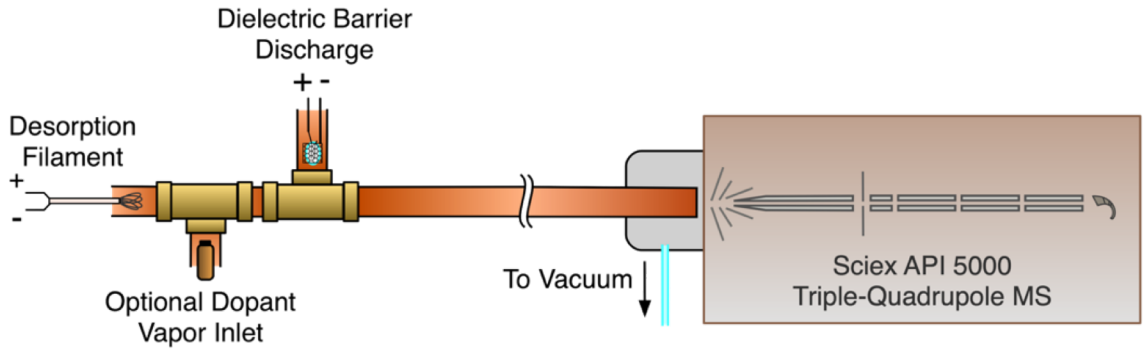

Figure 2.) Drug detection was accomplished on a triple-quadrupole MS system outfitted with a flow tube apparatus, a single-bulb dielectric barrier discharge ion source, dopant vapor inlet, and wire filament used for performing all desorption experiments.

A detailed instrumental schematic can be seen in Figure 2. Consisting of a sampling inlet, non-radioactive ionization source, atmospheric flow tube, and a mass spectrometer, the KRAFT-MS system shown in Figure 2 was used to characterize a range of CWA degradation products that contain a phosphorus atom at the center of a chemical functional group. In brief, an Agilent 6410A triple quadrupole mass spectrometer (Agilent Technologies; Santa Clara, CA, USA) was fitted with a custom ion inlet housing to permit the introduction of ions from a ~60 cm, 1-inch inner diameter copper tube with a dielectric barrier discharge (DBD) ion source fitted to the other end. A house vacuum pull of approximately 1 L/min was applied to the inlet housing so that reactant ions and other species could be drawn toward the mass spectrometer inlet. The DBD source used here was a simplified version of a four-bulb design previously reported. To circumvent the difficulty of fitting four individual DBD sources into two brass tees where electrical arcing can easily occur between sources or between the DBD source and the tube, this updated design combines the four individual sources into one large DBD ion source with voltage supplied

by a single pair of electrical leads. Along with the benefit of reducing the potential for arcing, the large DBD source ran on 15 V, and required only 80 mA of current in comparison to the previously reported 0.1 A when the DBD bulbs were powered separately. As illustrated in Figure 1, a small section of additional copper tubing with a 4 cm by 2 cm slit in the side was added at the front flow tube inlet. A light flow of purified nitrogen gas (99.9%, ~1 L/min) was directed along the long axis of the flow tube, as well. This created an area where residue samples on glass slides could be inserted under consistent conditions and where analyte signal could be enhanced due to the added nitrogen carrier gas.

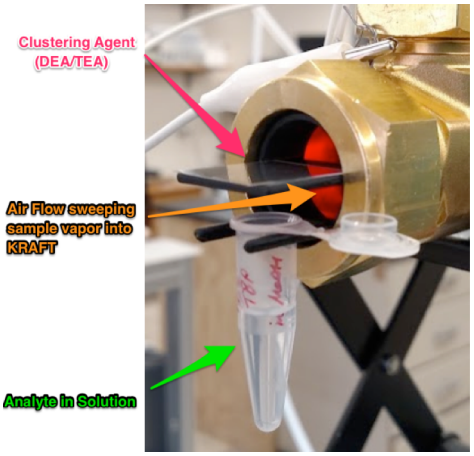

Figure 3. Current real-time sampling approach for non-contact analysis of soluble degradation products. The air sweeping over the sample carries vapor into the system where selective clustering is leveraged to create ions readily detected using mass spectrometry.

To illustrate the operational concepts of the KRAFT-MS system from a chemistry perspective there is merit in exploring the relative physical characteristics of a few analytes. With a standard vapor pressure of 1.1×10^{-3} Torr at 298 K, TBP has an inherently low maximum concentration that can be found within vapor. At room temperature, this corresponds to a maximum concentration of vaporized TBP that can be achieved above pure liquid TBP of approximately 10 ppm, so any methods that might be applied to trace TBP determination must be able to detect ppb levels or lower. In this regard, KRAFT-MS as an analytical technique has been shown to reach these levels for explosives, but had yet to be assessed for TBP or even in the positive mode of operation. To re-emphasize the mode of operation an image of the KRAFT inlet is shown in Figure 3.

Even though the protonated TBP species was visible in the KRAFT-MS system, simply monitoring this single species does not permit the addition of a second layer of selectivity added by using a dopant molecule to cluster with TBP. As Figure 1 illustrates, the clustering creates a larger *m/z* species which, under select circumstances, can place the target *m/z* range outside of the chemical noise. Trace amounts of the dopants in this case would be swept into the front of the flow tube concurrent with TBP samples, but not directly added to the TBP solutions. Only gas-phase dopant molecules reaching interacting with TBP in the flow tube would promote cluster formation. By this mechanism, dopants could easily be added externally to the flow tube sampling ambient air in non-laboratory settings and still produce the clusters, whereas this would not be feasible if the dopant-analyte clusters were to form primarily in solution. These clusters containing TBP and a dopant molecule form in a manner analogous to dimers formed between a pair of high proton affinity compounds bound with an interaction between a proton, which are known as proton-bound dimers. Although homodimers are common to observe, heterodimers can also readily form and would essentially describe the TBP-dopant clusters targeted by the KRAFT-MS analyses. Conceptually, the target dopant molecule that could lower detection limits in a charge-competitive system would be a compound with a decidedly higher proton affinity than the

target analyte. This would thereby allow the dopant to favorably abstract charge, but by selective clustering with the analyte, analytes that might otherwise not receive charge and go undetected may in fact become ionized. In the case of DEA, this is feasible because its proton affinity 952.4 kJ/mol exceeds an estimated proton affinity for TBP of 918 kJ/mol. Interestingly, this does not hold for pinacolyl methylphosphonate (PMP), which at an estimated proton affinity of 889 kJ/mol stands to be less able than TBP to become protonated. However, the TBP-PMP protonated cluster has been visible from the headspace vapor of a 1 ppb TBP solution, which is the lowest concentration standard used for the solution calibration curves.

CHEMICAL FAMILY	kJ/mole	Compound
Aromatic Amines	942	Trimethyl amine
Amines	930	Pyridine
Phosphorous compounds	898	DMMP
	891	Trimethylphophate
Sulfoxides	884	DMSO
	853	Ammonia
Ketones	832	2-pentanone
Esters	805	1-Hexene
Alkenes	789	Butanol
Alcohols	750	Benzene
Aromatics	691	Water
Alkanes	543	Methane

Table 1. *Reported proton affinities for select compounds and their associated chemical functional groups. The KRAFT-MS system combined with information from the ion mobility system provides a mechanism to probe the relative affinities for target compounds. Through this understand more selective clusters can be identified that maximize sensitivity for rapid assessment of compounds in environmental matrices.*

Table 1 illustrates the range of proton affinities for common analytes and functional groups. The results from our KRAFT-MS experiments using TBP and select charge carrying species establish a fundamental and outstanding question regarding gas-phase ion clusters: *What is the maximum difference in proton affinities between two species that still allow for stable heterodimer formation?* The answer to this question will provide the bounds to which selective clustering agents may be identified. The information presented in Table 1 can also aid in placing the traces shown in Figure 4 in context. The extracted ion chromatograms shown in Figure 4 correspond to experiments where the signal intensity for the phosphorus containing compounds is largely linear with changes in TBP solution concentration. An initial examination of these traces also reveals the largely consistent baseline ion current, which lends merit to the technique even using positive ion monitoring, which is substantially less clean than negative ion mode due to the higher abundance of compounds with high proton affinities rather than high gas phase basicities. It is important to note that the absolute detection limits for these experiments remain difficult to state precisely due to the nature of the system when sampling non-equilibrium vapor concentrations. The concentrations listed on the x-axis are the solution phase concentrations of the analytes and it is only the vapor emitted during the experimental time frame that is detected using selective ion-neutral clustering.

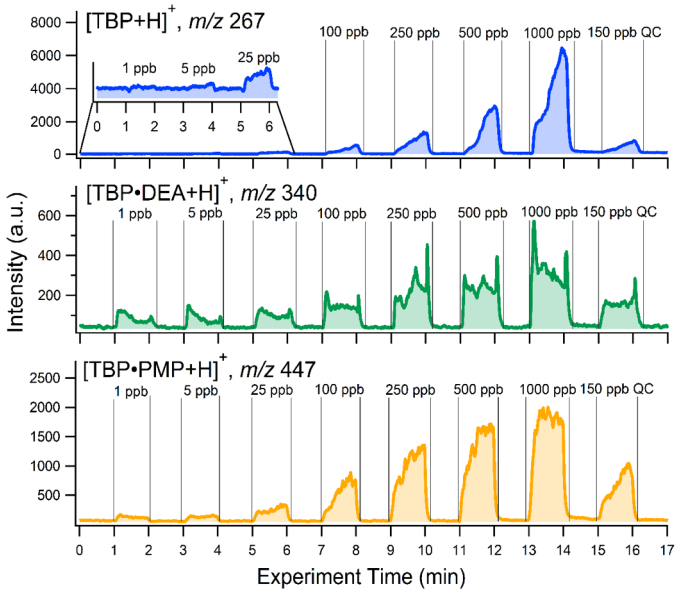

Figure 4. *Tributyl phosphate traces obtained with standard solutions of concentration 1, 5, 10, 25, 100, 250, 500, 1000 ppb in solution. Analysis times of 1 minute per sample were used with 1 minute background equilibration before and between each sample. It is worthy to note that the concentrations listed are those for the solution. The concentrations measured using the KRAFT-MS system are solely from the non-equilibrium vapor concentrations above the solution and represent concentrations by volume that are approximately an order of magnitude less.*

Thermodynamic Assessment of Gas-Phase Clusters using KRAFT-MS

To transition the KRAFT-MS efforts from an observational approach to a quantitative thermodynamic understanding of the cluster, the mass spectrometry experiment used for the KRAFT coupling was altered to incrementally increase the energy of ions traversing the system. By monitoring the relative intensity changes as a function of energy (i.e. a survival yield curve) it is possible to deduce thermodynamic characteristics. Moreover, understanding the thermodynamics of the cluster can also inform the identification of optimum clustering reagents for a target analyte. Using this foundation as a guiding principle would suggest the target dopant molecule (i.e. the reactant ion) most capable of lowering detection limits in a charge-competitive system would be a compound with a decidedly lower proton affinity than the target analyte.

To evaluate the relative proton affinities of the target compound classes a series of survival curve experiments were conducted with the newly assembled KRAFT-triple quadrupole mass spectrometer. Figures 5 and 6 outline the experimental approach that compares the relative SY curves between different clusters which allows relative proton affinities to be deduced. To illustrate this principle a qualitative comparison of proton-bound dimerization of TBP and select OPC was performed with selected amines. The clustering agents triethylamine, tributylamine, and hexylamine were chosen for their higher PA values relative to TBP, while DMMP was included as an additional OPC for cluster formation

because its experimentally determined PA values are close to, but less than the PA estimate for TBP. With experimental PA values between 902 kJ/mol and 911 kJ/mol for DMMP, TBP should exhibit a higher precursor ion survival than DMMP when paired with TEA, TBA, and hexylamine for survival yield analysis.

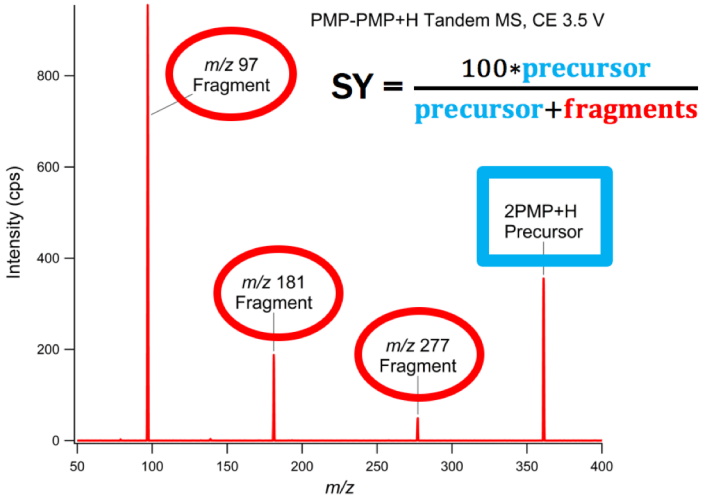

Figure 5. Example of the survival yield method using the triple quadrupole mass spectrometer. In this experiment at any given collision energy (i.e. fragmentation energy), the ratio of the target precursor ion intensity is compared to the range of fragment ions observed. By plotting the SY against collision energy a curve is produced which provides a metric to assess the stability of a given cluster.

Assuming stability patterns are solely a function of ΔPA, the expected trend was observed for both TBP and DMMP (Figure 5). Examining the relative interaction strengths for each OPC with different amines indicates cluster stability increases as a function of decreasing ΔPA following an order of OPC-hexylamine > OPC-TEA > OPC-TBA. When comparing the interaction strengths of TBP to DMMP with a given amine, TBP-amine > DMMP-amine. This is consistent with the assumption that TBP has a greater PA than DMMP and a stronger binding energy with the amines used. One similarity among the 6 dimeric species was that the predominant fragment was the intact protonated amine species, confirming that TEA and TBA both have higher proton affinities than TBP and DMMP. Published ion thermochemistry data provides an excellent resource for proton-bound dimer trends involving straightforward organics such as amines, alcohols, aldehydes, and ketones, but without this information for OPCs, predicting suitable dopants may be difficult. It is worthy to note that through these experiments a noticeable gap in the published literature exists with respect to OPC thermochemistry. In collaboration with Dr. Ben Bythell (Ohio University), it was possible to computational verify the experimental results and contribute to the existing literature regarding the thermochemistry of OPCs. The outcome of this exercise is shown in Figure 7 which compares the respective calculator proton affinities to the experimental values with R^2 values of >= 0.93. Recognizing that computational efforts to calculate proton affinities are particularly problematic in some cases this level of agreement suggests that our values are well aligned with contemporary methods

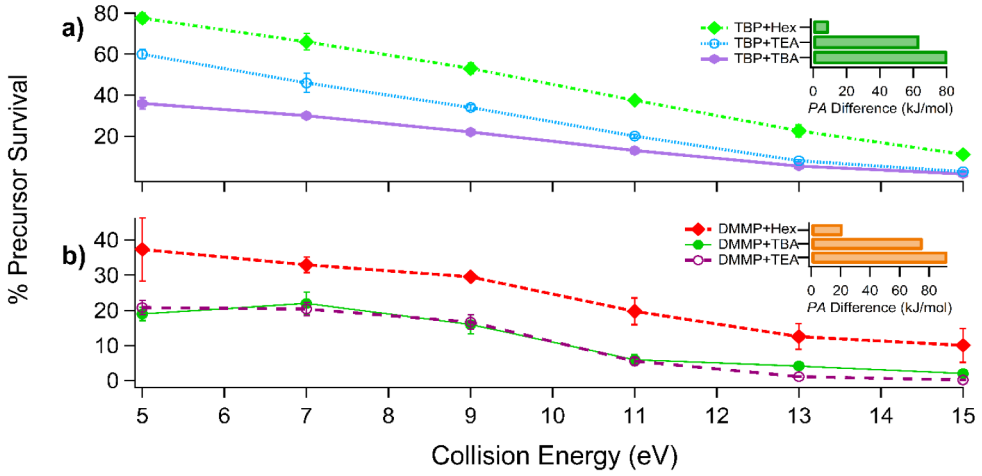

Figure 6. Survival yield trends for precursor dimer species were observed for a) tributyl phosphate and b) dimethyl methylphosphonate in combination with tributylamine and triethylamine, and hexylamine. The survival yield experiments were performed to bracket the proton affinity of tributyl phosphate, which has no reported experimental PA value. While the estimated PA for tributyl phosphate is about 918 kJ/mol, the SY trends examined here may suggest a higher value of proton affinity for TBP.

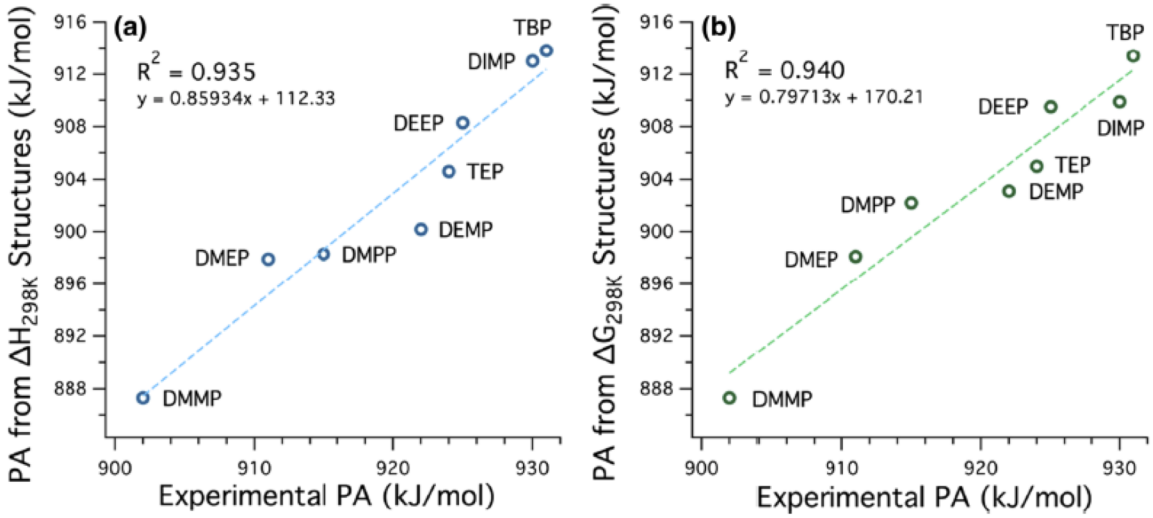

Figure 7. Linear regression of the comparison between experimental proton affinities and proton affinity values computed using the lowest-energy (a) ΔH298 K and (b) ΔG298 K structures for the select phosphonates.

Thermodynamic Characterization of Selective Clustering using Ion Mobility-Mass Spectrometry

The experiments with the KRAFT-MS system, though extremely important, are constrained by the relatively flexibility of the apparatus. To explore a series of well-controlled experimental variables including reactant ion concentration and reaction time, a different apparatus is required. Figure 8 contains a schematic of the ion mobility-linear ion trap system equipped with a drift gas modifier unit. This system allows a unique set of ion mobility experiments to be conducted in which the same proton-bound heterodimers formed in KRAFT-MS can be probed in more depth. In tandem with the KRAFT-MS efforts this project also yielded the developed of a quantitative model that describes the degree and type of selective ion-neutral interaction that supports the low detection limits seen in the KRAFT-MS system. Moreover, there were some unanticipated analytical benefits realized through these experiments; namely, enhanced separation efficiencies for a chemical warfare agent simulant (dimethyl methyl phosphonate (DMMP)) and a common CWA degradation product (methyl phosphonic acid (MPA)) when using ion mobility spectrometry as a field detector.In a traditional ion mobility spectrometer the gas flow occurs in the direction opposite to the ion flow with the latter being driven by an electric field.

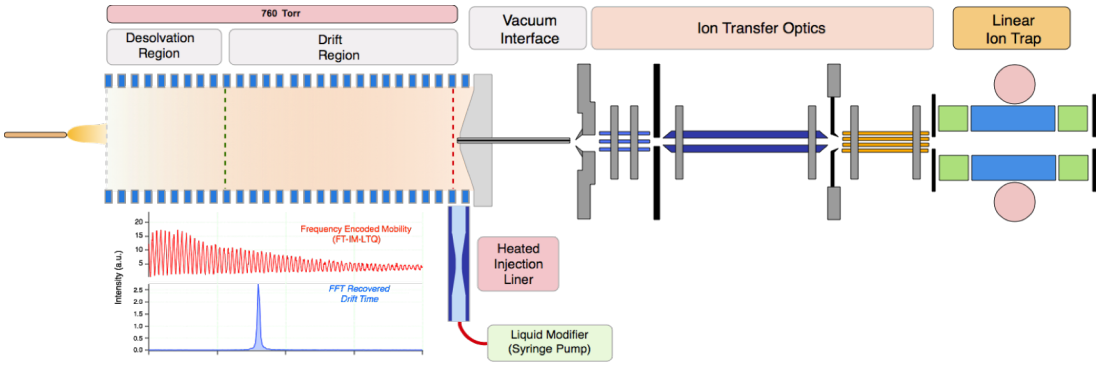

Figure 8. *Schematic representation of the atmospheric pressure dual gate ion mobility system coupled with a LTQ mass spectrometer. Mobility spectra may be acquired using either the integrated Faraday plate or by encoding the mobility data in the frequency domain. For the latter, the FFT may be used to identify the mobility distributions of m/z selected ion populations. Drift gas modifiers are introduced into the counter-current drift gas using a syringe pump and a temperature controlled heated injection liner.*

In Figure 8, ions generally move from left to right while the gas flow in the atmospheric pressure portion of the IMS from right to left. By adding a drift gas modifier, in this case, 2-propanol, it is possible to directly assess any changes in ion residence time, which by extension is a proxy for the degree of ion-neutral clustering that occurs. As stated earlier, not only does this shift provide a means of probing ion cluster thermochemistry but also may provide additional analytical benefits. As the data in Figure 9 illustrate, the shifts in drift time between 2-propanol and the target OPCs was both selective and substantially different between DMMP and MPA to realize the separation of these two analytes. Given

that ion mobility spectrometry is widely used in the field for the detection of CWAs and their degradation products this approach may prove useful in that domain. To provide more context to Figure 9, 2-propanol was introduced into the countercurrent drift gas via a glass capillary coupled to a temperature-controlled GC injection liner at a variable flow rate from 5 µL/hr to 160 µL/hr using a syringe pump. For the temperature and pressure conditions of the IMS cell, the gas phase concentration for 2-propanol at the flow rate of 5-160 µL/hr corresponds to a saturation ratio of S = 0-6.5x10^{-5}. Saturation ratio is defined as the vapor pressure divided by the saturation pressure, which is equivalent to the number concentration of vapor molecules divided by the equilibrium number concentration (derived via the Clausius-Clapeyron equation). To avoid the potential for temperature gradients in the IMS drift cell, the drift gas mixing chamber was held at the same nominal temperature as the mobility drift cell (~175 ºC).

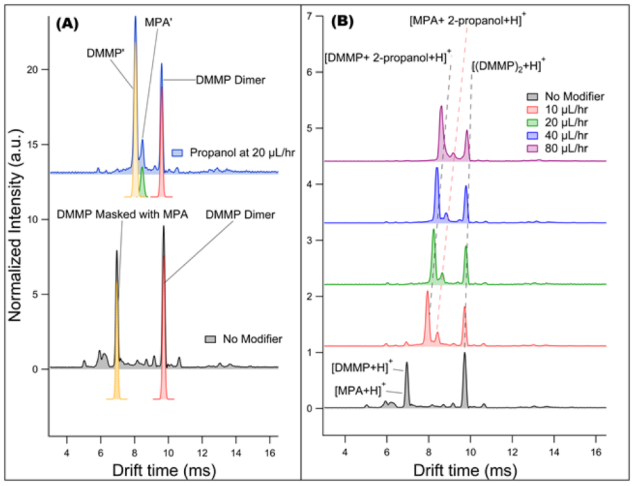

Figure 9. (A) *Faraday plate ion mobility spectra with (top trace) and without (bottom trace) 2-propanol as a modifier. The offset peaks were m/z identified using the instrument shown in Figure 3. The separation factors, alpha, for the peaks corresponding to DMMP and MPA illustrate that without the modifier the two species are indistinguishable.* ***(B)*** *Mobility separations of DMMP and MPA as a function of increasing drift gas modifier concentration. The stability of the proton-bound dimer of DMMP compared to the MPA and DMMP monomers illustrate the selective interactions between the ion populations and the modifier.*

With respect to the KRAFT-MS measurements and the target goal of realizing high degrees of selectivity and sensitivity it was our express intent to quantify the strength of the gas-phase clusters formed using the IMS-MS experiment. These data would further support the development of a quantitative model that can accurately reproduce shifts in the mobility domain as a function of drift gas-modifier concentration. Interestingly, the degree of mobility shift is directly related to the strength of the interaction between a target ion and is pairing neutral species and serves as yet another metric to quantify the strength of interactions between a target analyte and a range of potential pairing reagents. The following section details the model developed under this ARO effort that extends broadly to all ion-neutral clustering reactions in IMS systems.

$$\frac{K_{obs}}{K_0} = \frac{1 + \frac{K_1}{K_0} Sexp\left(-\frac{\Delta G}{kT}\right)}{1 + Sexp\left(-\frac{\Delta G}{kT}\right)} = \frac{\Omega_0 \mu_1^{1/2}}{\Omega_1 \mu_0^{1/2}}$$

Equation 1. *Relationship between the ratio of the observed mobility shift (K_{obs}/K_0), the concentration of the vapor phase modifier or pairing neutral, and the free energy of association (ΔG). It is through these experiments that we can link ion mobility measurements with selective clustering reagents in the KRAFT-MS experiment.*

Analyte Ion	Experimental CCS	Theoretical CCS	Reduced Mass
$[MPA+H]^+$	91.80 +/- 0.07	91.79	21.73
$[MPA+2\text{-}Propanol+H]^+$	119.12 +/- 0.19	123.57	23.76
$[DMMP+H]^+$	89.10 +/- 0.07	95.05	22.88
$[DMMP+2\text{-}Propanol+H]^+$	112.21 +/- 0.26	121.48	24.32

Table 2. Comparison of experimentally determined ion-neutral cross sections (derived from reduced mobility values) and those computationally determined. The high degree of similarity provides evidence to support further development of a predictive clustering capacity.

Equation 1 mathematically links the ratio of the observed mobility shift *(K_{obs}/K_0)*, to the free energy of association (ΔG) or the strength of the gas phase interaction. While we can measure these values explicitly for each target ion cluster, the opportunity exists through advances in computational modeling to develop a predictive capacity. In Equation 1 there are a range of experimental variables that are either measured or controlled including temperature, a cluster ion's mobility, its reduced mass, and the saturation ratio (S) of the coordinating vapor. There is one parameter though, Ω_1, that corresponds to the ion-neutral cross section, for the target ion clustered with one vapor molecule that is unknown. This parameter remains unknown, even through experiment, as a complex equilibrium exists between the different cluster forms. Stated differently, once the conditions exists for which an ion pairs with a single neutral vapor the probability that a second neutral vapor also begins to associate also increases. Because this complex equilibrium exists computational assistance is required.

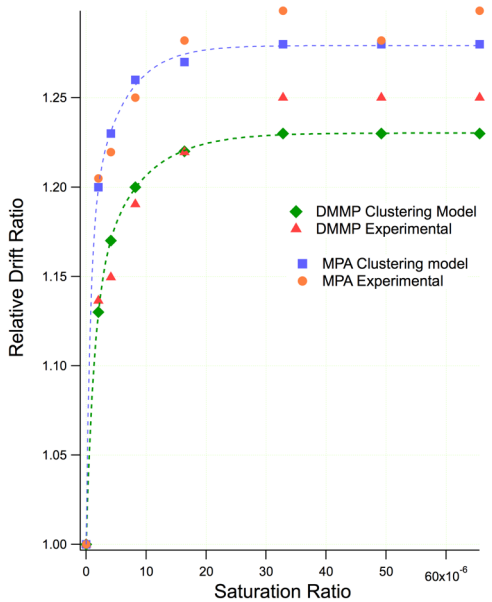

Figure 10. *Correlation between the experimentally determined mobility shifts as a function of drift gas modifier concentration (i.e. Saturation Ratio) and the shifts predicted by the clustering model numerically described in Equation 1.*

To compute ion-neutral collision cross sections we utilized the collision cross section calculation package IMOS (v1.06b, http://www.imospedia.com/imos/, Larriba & Hogan 2013 J. Phys Chem A, J. Comput. Phys). In IMOS, each atom was modeled as a sphere with its radius equivalent to its van der Waals radius. Colliding gas molecules were modeled as spheres with radii of 0.3 nm and collision cross sections were calculated using both the diffuse and elastic scattering methods at the measurement temperature (175°C), with the

ion-induced dipole considered between the excess proton and the impinging nitrogen gas molecules (with a polarizability of 1.7 A^3). As the data in Table 2 indicate, there is strong agreement between the experimentally measured mobilities for the cluster ions and those found computationally. Using the values in Table 2 combined with controlled experimental variables in Equation 1, it is possible to evaluate the performance of the model across a range of gas-phase modifier concentrations.

Graphically this approach yields the relationship between theoretically predicted mobility shifts and those observed experimentally shown in Figure 10. Though not shown, there are error bars for the experimental data points. It is also noticeable that there is a deviation from a computational perspective at higher vapor modifier concentrations. It is our working hypothesis that these deviations are due to the fact that we have not fully optimized the computation structure for the target ion with coordinated with two vapor molecules. Nevertheless, the strong agreement at the low vapor phase modifier concentration is highly encouraging and it marks the first, largely, successful approach to quantify polyatomic ion neutral clustering in an ion mobility spectrometer.

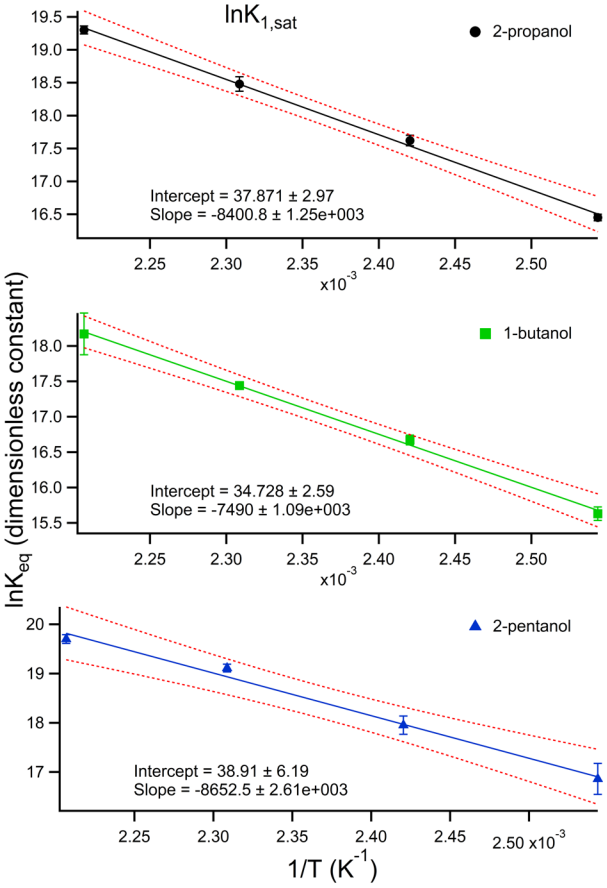

Figure 11. van't Hoff plot comparing the natural log of the equilibrium constant as a function of inverse of temperature for the clustering of 2-propanol with the target analyte ion. The inferred equilibrium constants (calculated from Gibbs free energy (ΔG) inferred at variable saturation state) for 80, 120 and 160 µL/hr were averaged and plotted with error bars.

Most importantly, by adjusting the temperature of the IMS-MS system while monitoring the degree of mobility shifts it is possible to derive classical van't Hoff plots for each ion neutral cluster (See Figure 11) which presents an wholly new method to probe gas-phase ion neutral interactions. The broad applicability of this method has been broadly extended beyond the scope of this ARO efforts and is considerable contribution to the field.

Representative Results and Applications Integrating KRAFT-MS

KRAFT Evaluation of Thiodiethanol. Thiodiethanol (TDE) is a particularly versatile compound in relation to the chemical weapon, sulfur mustard (HD). Along with being a main degradation product of HD, TDE can also be used as a simulant for developing methods to detect HD and as a precursor species to HD that can be indicative of illicit preparation of chemical weapons. Direct detection of the thiodiethanol species in vapor is an objective met with several attempts at non-contact residue detection, but existing methods have undesirably high detection limits in the gas phase (>ppm) and are predominantly non-specific approaches that do not provide the certainty afforded by mass spectrometry. Building upon prior efforts using the KRAFT system, we demonstrate the potential of AFT-MS for ultra-trace, non-contact residue analysis based upon TDE vapor sampling and nitrate interaction chemistry.

Prior publications regarding trace MS analysis of thiodiethanol, such as the vapor analysis using DBD ionization by Wolf et al. and Ni^{63} ionization by Crawford et al., frequently monitor protonated TDE. Unfortunately, the proton affinity of thiodiethanol is quite low relative to the numerous possible interfering species that may be present in any given laboratory environment due to off-gassing, such as amines; Midey et al. reported a computationally-derived proton affinity of 833 kJ/mol for the sulfur atom on thiodiethanol. This low proton affinity of TDE results in little probability that thiodiethanol molecules can preferentially abstract protons for sufficient ionization within variable environments. Additionally, monitoring the intact protonated TDE species can be challenging even with a soft ion source like DBD because the loss-of-water fragment ion is readily formed. Prior work by Morrison and Clowers postulated that the presence of hydroxyl groups on alkylphosphonic acids

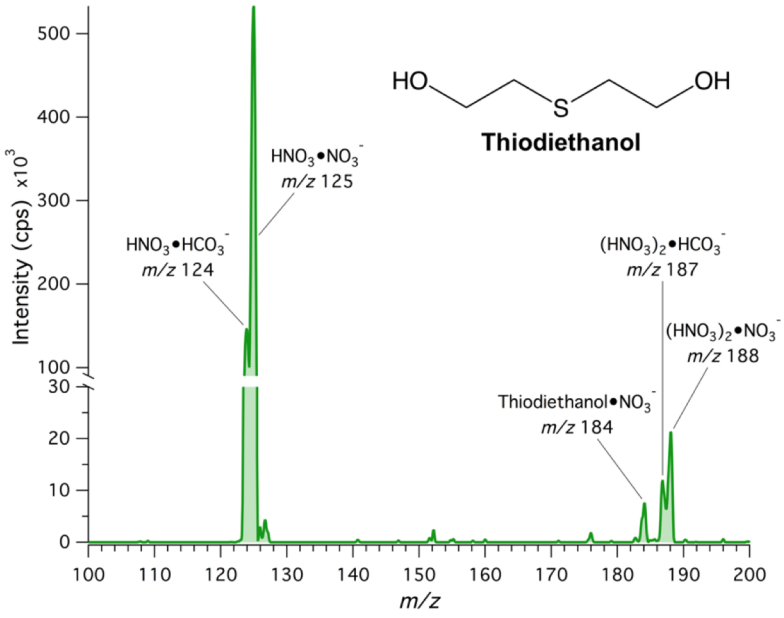

Figure 12. The targeted CWA simulant species—thiodiethanol—can be seen at *m/z* 184 as a nitrate adduct within AFT-MS mass spectra along with reactant ions $HNO_3{\bullet}HCO_3^-$, $HNO_3{\bullet}NO_3^-$, $(HNO_3)_2{\bullet}HCO_3^-$, and $(HNO_3)_2{\bullet}NO_3^-$.

may facilitate cluster formation with nitrate, so exploring the possibility of nitrate interaction with TDE was the route taken to circumvent difficulty of protonation resulting from the low TDE proton affinity and potential fragmentation from instability of the protonated species. As shown in Figure 12, a low but measurable signal for TDE adducted with nitrate (*m/z* 184) can be observed from sampling the vapor from a container of neat TDE with the lid slightly cracked. These data combined with the efforts to stability clusters of opioids illustrate the applicability of the approach to identify select gas-phase clusters. These data directly supported the efforts pursued under Specific Aim 3. While only a limited set of examples are provided here, additional detection limits for select target reagents can be found in the associated publications and prior annual reports.

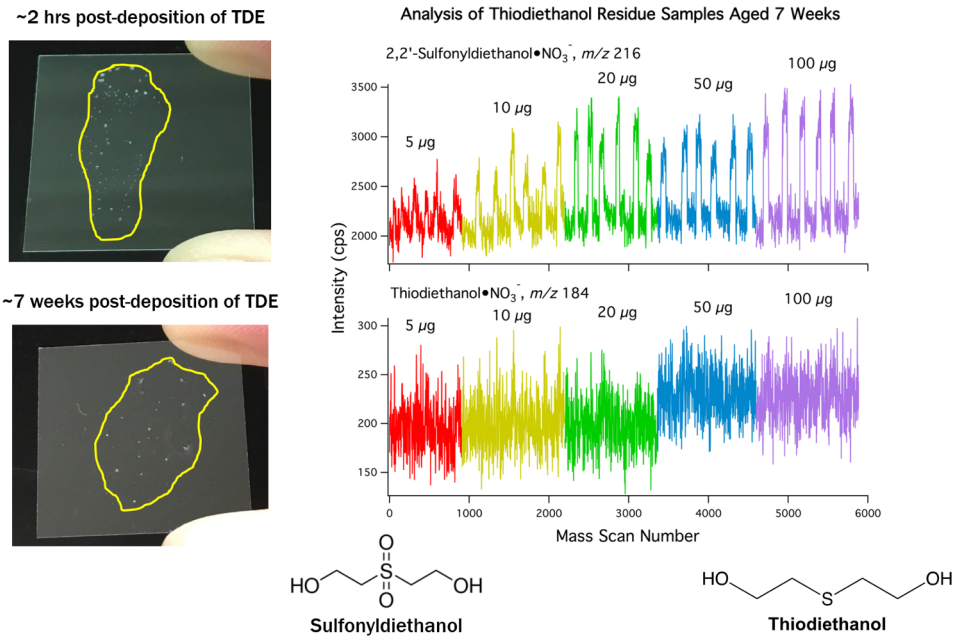

Figure 13. a) As a preliminary assessment of the aged thiodiethanol residues, one of the 100 µg residue samples was analyzed using SIM on *m/z* 184, 200, and 216, which correspond to the nitrate adducts with thiodiethanol (TDE), thiodiethanol sulfoxide (TDO), and thiodiethanol sulfone (TDOO), respectively. **b)** The entire set of aged 1-100 µg TDE residue samples was then analyzed, but only monitoring *m/z* 184 and 216 for enhanced sensitivity. **c)** A visual comparison of a 10-µg TDE residue merely two hours after sample deposition with a seven weeks post-deposition 10-µg TDE residue reveals the transformation of an analyte that is liquid at room temperature (i) to degradation products that are crystalline solids at room temperature (ii).

For quantitative work with minute residues of TDE, a sampling approach with the AFT-MS was devised where the TDE was deposited on small glass coverslips. These coverslips can then be held within the partially open flow tube that has both a vacuum pull and a light flow of nitrogen over the sample to assist the mass transport through the flow tube. The headspace vapor from the TDE liquid residues is then conveyed down the flow tube for ionization and mass analysis. Saturated vapor pressure of TDE at 298 K is 0.49 mTorr, and under the typical ambient pressure of ~690 Torr at Washington State University in Pullman, WA the maximum vapor concentration of thiodiethanol is ~3 ppm. However, in the dynamic vapor sampling environment of an atmospheric flow tube system,

the very low mass TDE residues cannot create a saturated system. Correspondingly, the mass spectrometric system must be capable of sub-ppm analyte detection out of vapor.

While the exact vapor concentrations produced by each sample mass is challenging to determine under the conditions used, it is certainly feasible to approximate TDE residue mass by simple vapor sensing with appropriate calibration curves. A sample mass range covering 1-100 µg and the two quality control samples of 3 µg and 30 µg underwent non-contact analysis to yield the ion current traces displayed in Figure 13. The linear range identified from this experiment was found to include the full set of 1-100 µg calibration samples, which produced an R^2 of 0.959. Additionally, the mean analyte masses for the quality control samples as found by the calibration curve had a reasonable initial degree of accuracy for non-contact detection (5 ± 5 µg for the 3 µg QC, 34 ± 19 µg for 30 µg QC). However, the signal variability and resulting precision issues indicate the need to further investigate the primary contributions to signal differences between replicate samples for the same applied residue mass.

Sources of Signal Variability for Trace Residue Analysis. At the outset of this experiment, we anticipated that the total solution volume was one such parameter that would contribute to signal variability. The solution volumes were maintained at 5 µL for all TDE residue masses with this in mind. However, the ion current obtained between sample replicates for the same mass displayed more variation than initially expected (Figure 6). One probable source of the signal fluctuation could be from the residue sample preparation; variation in the surface area of residues very likely could alter the absolute quantity of analyte mass vaporizing at any given moment. Even taking care to maintain consistent analyte solution application, the unpredictability of localized analyte clustering after solution deposition renders this a difficult task. Furthermore, this gets to be a bigger problem as the analyte quantity increases; the smaller analyte masses (1 µg up to ~20 µg) are spread more uniformly as the solution is applied to the glass slide and create a larger surface area per analyte quantity. Moving on to the larger analyte quantities, there are visible droplets of analyte that start to become apparent; the more that the liquid analyte residue forms these larger droplets after the solvent has evaporated, the more likely it is that the increased quantity of analyte will not produce a directly corresponding increase in signal. Beyond about 20 µg, the behavior observed is that the analytical sensitivity sharply drops off relative to the 1-20 µg residue range. Though not shown, additional experiments were conducted to evaluate the role of deposited surface area on the observed signals which indicates that this parameter also plays a significant role. Despite these challenges, detection of trace levels of TDE vapor was readily detectable using KRAFT-MS

KRAFT Detection Limits for Opioids. In a fashion similar to the efforts to quantify TDE, a separate analytical campaign was initiated focusing on the challenge associated with real-time, non-contact detection of opioids using KRAFT-MS. Figure 14 shows the range of analytes used to demonstrate experimental feasibility and probe the underlying chemistry of ion-neutral clustering with respect to options. The data for these experiments using TBP clusters is shown in Figure 15 illustrating impressive levels of detection from a real-time analysis system.

Using the survival yield method described in the paper by Morrison et al.[https://doi.org/10.1007/s13361-019-02202-w], a renewed effort was placed on the survival characteristics of select opioid clusters. Early efforts in this project described some initial results however, closer investigation of the clustering behavior between tri-buty phosphate and select opioids illustrated the importance of both matching the respective proton affinities and the role of steric hindrance on the stability of the cluster. Some of compounds shown in Figure 14 were chosen based upon their structural characteristics and not necessarily due to their role as a narcotic. Close examination of the structure of cocaine illustrates that the chair confirmation combined with the amine and ester groups is necessary to form a stable cluster. A detailed examination of the structures illustrates that the distance between the amine and the carbonyl group in tetracaine is larger than the respective distance of these functional groups in cocaine which hinders the reduces the capacity of the system to form a stable gas-phase cluster with TBP. As a result, the stability of the tetracaine is diminished as shown by the survival yield curve. As Figure 15 illustrates impressive levels of detection are realized using the KRAFT-MS system and selective ion-neutral clustering. Given the challenge of non-contact detection with respect to select opioids (e.g. fentanyl) and the public health impacts, including on first responders, identifying highly sensitive routes of detection remain highly relevant.

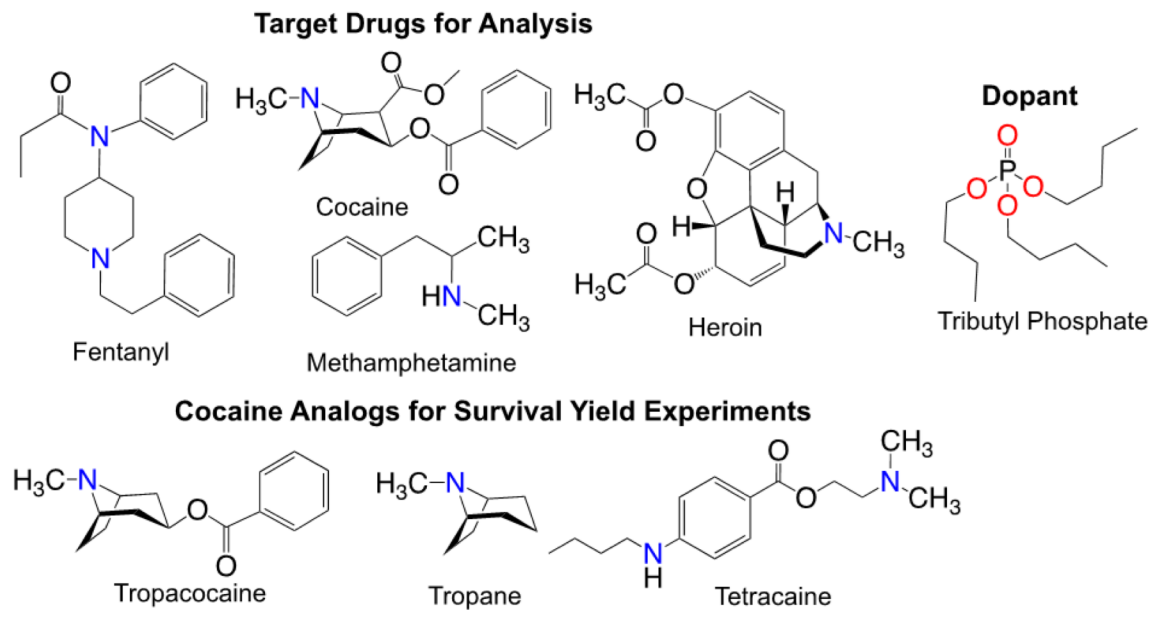

Figure 14. Select opioids and opioid analogues used to probe hypotheses regarding the salient interactions governing the formation of stable gas-phase clusters that maximize sensitivity for non-contact sampling.

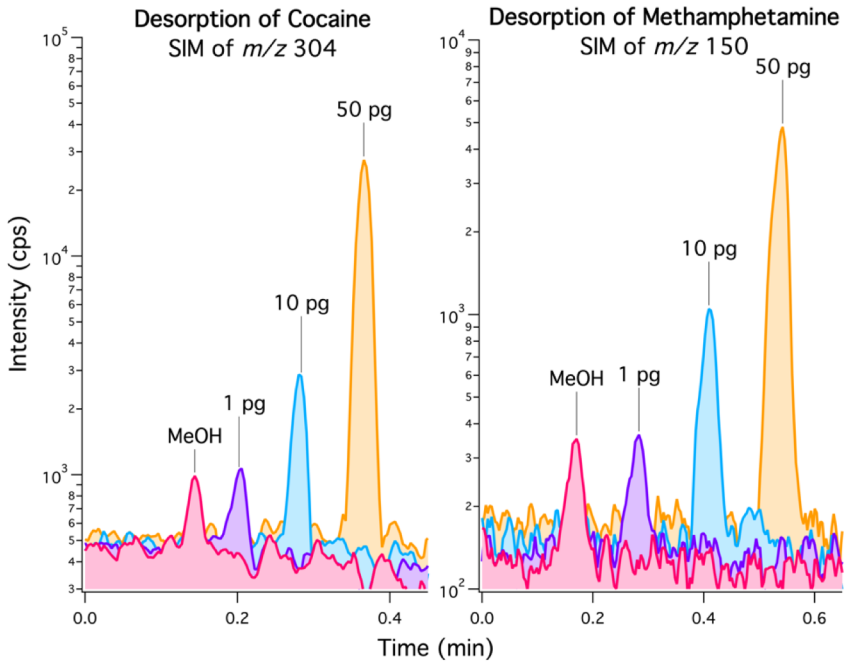

Figure 15. Using the KRAFT system and a thermal desorption apparatus the detection limits of cocaine and methamphetamine was probed as TBP clusters. These data illustrate that the single digit picogram levels there is little difference between the spiked and blank sample (MeOH). However, at 10 pg, a clear signal was obtained for both species. This more than an order of magnitude more sensitive that current approaches using cloth/filter swipes in the field.

Training and Mentorship

The funding supplied by ARO under this effort supported 3 graduate students in chemistry at from Washington State University:

Pearl Kwantwi-Barima, Ph.D. – Clowers Group – Graduation Date: 2020
Kelsey Morrison, Ph.D. – Clowers Group – Graduation Date: May, 2019
Peyton Nosbusch, M.S. – Clowers Group – Graduation Date: May, 2018

Kelsey Morrison completed an exemplary graduate school career in May 2019 and is currently employed in the National Security Directory at Pacific Northwest National Laboratory focusing on trace threat detection. Though a different candidate was selected for the award, Kelsey was also a finalist for the Linus Pauling Distinguished Post-Doctoral Fellowship. This award process was extremely rigorous and required multiple rounds of interviews and presentations. It is also worthy to note that Dr. Morrison published 9 first-author manuscripts as a graduate student and is poised to realize a total of 13 publications during her time at WSU. Support from ARO was integral in training and success, ultimately leading to the start of a career in national-security and analytical chemistry.

Pearl Kwantwi-Barima completed her degree focusing on the core fundamentals of gas-phase clustering interactions. In addition to making key instrumental improvements, Pearl has expanded the range of compounds explored using the newly developed clustering model (initially reported in Year 2) to a range of other compounds. Dr. Kwantwi-Barima published 5 first-author manuscripts with support from ARO and is currently a post-doctoral researcher within the National Laboratory complex.

Technology Transfer and Dissemination

Collaborations with Pacific Northwest National Laboratory continue with regards to the development of the KRAFT system to understand complex proton bound heterodimers. Multiple joint publications have resulted from the combined efforts and their pursuit of the KRAFT-MS. In fact, PNNL continues to build on these fundamentals of this ARO effort and the pursuit of this technology was awarded the R&D 100 Award in 2019 (https://www.pnnl.gov/about/rd-100-awards). A joint publication was realized between WSU and PNNL in this period of performance and with the transition of Dr. Morrison to that organization collaborative efforts are expected to continue.

Attributed Publications

1. Morrison, K.A., Clowers, B.H.: Non-contact detection of thiodiglycol vapors and associated degradation products using atmospheric flow tube mass spectrometry. Analyst. 146, 3263–3272 (2021)

2. Morrison, K.A., Valenzuela, B.R., Denis, E.H., Nims, M.K., Atkinson, D.A., Clowers, B.H., Ewing, R.G.: Non-contact vapor detection of illicit drugs via atmospheric flow tube-mass spectrometry. Analyst. 145, 6485–6492 (2020)

3. Kwantwi-Barima, P., Hogan, C.J., Jr, Clowers, B.H.: Probing Gas-Phase-Clustering Thermodynamics with Ion Mobility--Mass Spectrometry: Association Energies of Phenylalanine Ions with Gas-Phase Alcohols. J. Am. Soc. Mass Spectrom. 31, 1803–1814 (2020)

4. Kwantwi-Barima, P., Reinecke, T., Clowers, B.H.: Enabling resolution of isomeric peptides using tri-state ion gating and Fourier-transform ion mobility spectrometry. Int. J. Ion Mobil. Spectrom. 23, 133–142 (2020)

5. Kwantwi-Barima, P., Reinecke, T., Clowers, B.H.: Increased ion throughput using tri-state ion-gate multiplexing. Analyst. 144, 6660–6670 (2019)

6. Morrison, K.A., Bythell, B.J., Clowers, B.H.: Interrogating Proton Affinities of Organophosphonate Species Via Atmospheric Flow Tube Mass Spectrometry and Computational Methods. J. Am. Soc. Mass Spectrom. 30, 1308–1320 (2019)

7. Kwantwi-Barima, P., Hogan, C.J., Jr, Clowers, B.H.: Deducing Proton-Bound Heterodimer Association Energies from Shifts in Ion Mobility Arrival Time Distributions. J. Phys. Chem. A. 123, 2957–2965 (2019)

8. Morrison, K.A., Ewing, R.G., Clowers, B.H.: Ambient vapor sampling and selective cluster formation for the trace detection of tributyl phosphate via atmospheric flow tube mass spectrometry. Talanta. 195, 683–690 (2019)

9. Davis, A.L., Reinecke, T., Morrison, K.A., Clowers, B.H.: Optimized Reconstruction Techniques for Multiplexed Dual-Gate Ion Mobility Mass Spectrometry Experiments, http://dx.doi.org/10.1021/acs.analchem.8b04175, (2019)

10. Morrison, K.A., Clowers, B.H.: Characterization of alkylphosphonic acid vapors using atmospheric flow tube--ion trap mass spectrometry. Rapid Commun. Mass Spectrom. 32, 1363–1371 (2018)

11. Kwantwi-Barima, P., Ouyang, H., Hogan, C.J., Jr, Clowers, B.H.: Tuning mobility separation factors of chemical warfare agent degradation products via selective ion-neutral clustering. Anal. Chem. 89, 12416–12424 (2017)