Final Report

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Project Description and Final Report:

I. Project Objectives

The PI's involvement with the Separations and Analysis Program in OBES began with his appointment as a Wigner Fellow at Oak Ridge National Laboratory in late 1983. He was involved in the organic mass spectrometry effort and, over time, served as the Organic Mass Spectrometry group leader and section head of the Analytical Spectroscopy Section. In the fall of 1999, he was named ORNL Scientist of the Year for his contributions to organic mass spectrometry. In January, 2000, he moved to Purdue University with the major motivation being the opportunity to work with aspiring scientists (i.e., graduate students and post-docs). He was invited to submit a proposal to the OBES by the separations and analysis program managers at that time. The overall objectives of this research effort have been to expand the capabilities of mass spectrometry for the structural characterization of polyatomic ions of relevance to the broad mission of the Department of Energy. Mass spectrometry currently plays an important role in virtually all of the molecular sciences by virtue of the value of the accurate measurement of mass and the structural information that can be derived from various structural probes based on, for example, ion chemistry, ion mobility, and ion

spectroscopy. Mass spectrometry has long played important roles in supporting the missions of the Department of Energy and its predecessor agencies. The original role of mass spectrometry, of course, was in the area of isotopic analysis of nuclides. However, molecular mass spectrometry has played increasingly important roles is many aspects of the production and use of energy as the nation has diversified its energy portfolio. Indeed, molecular mass spectrometry applications have come to dominate the use of the powerful array of techniques that are currently referred to collectively as "mass spectrometry". There is an ongoing need for the expansion of the measurement capabilities associated with molecular mass spectrometry that involves both technological developments as well as improved understanding of the chemical and physical processes that take place upon ionization, ion reaction, and ion analysis in a mass spectrometer. Advances in mass spectrometry have impacted science broadly and further advances will be required to meet the needs of current energy and environmental research.

This program historically focused on the structural characterization of polyatomic ions, usually within the context of a tandem mass spectrometry experiment. A wide variety of physical and chemical processes can take place within a mass spectrometer and advantage can be taken of such processes to enhance the quality and quantity of information that can be derived for a given chemical system of interest. For example, ions can undergo interactions with neutral molecules/atoms, light, surfaces, electrons, or oppositely charged ions. The outcomes of all such interactions can be sensitive to the structures of the ions and are therefore candidates for probes of ion structure. This program has historically focused on the chemistry and physics associated with ion/neutral interactions at both low and high translational energies, and ion/ion reactions. The former area has involved the study of ion/molecule reactions at thermal energies and the extensive study of collisional activation under a wide variety of conditions. A major area of emphasis has been collisional activation in electrodynamic ion traps. The study of gas-phase ion/ion reactions within the context of tandem mass spectrometry was initiated in this program and has grown to be a major research area in this group. Most of the focus in ion/ion chemistry has been on proton transfer and electron transfer reactions but the discovery of selective covalent chemistries has opened up many new lines of inquiry. Molecular mass spectrometry has undergone remarkable changes in the last few decades with major breakthroughs in ionization, ion chemistry, ion mobility, ion spectroscopy, mass analysis, etc. The power and reach of mass spectrometry continues to grow at a rapid pace, largely fueled by new discoveries and deeper fundamental understanding of the underlying chemistry and physics. Developments in this program have significantly contributed to the remarkable development of mass spectrometry over the past few decades.

II. Background and Significance

The information available from a conventional mass spectrometry experiment can derive both from the accurate measurement of mass and from the measurement of ion abundance. The former measurement generally provides information regarding analyte identity (i.e. it addresses the question, "What is it?") while the latter measurement provides information regarding analyte abundance (i.e., it addresses the question, "How much?"). As the mixtures of interest become increasingly complex, as in analyses relevant to bio-fuels, and as the molecular species of interest themselves have become increasingly complex (e.g., multiple possible isomeric forms), new and improved tools for structural characterization are needed. That is, the measurement of mass alone cannot fully address the question "What is it?". Historically, ion chemistry has been used to

improve the specificity of a molecular mass spectrometry experiment. Fragmentation reactions, in particular, are generally the first option in addressing ion structural characterization challenges [1]. One or more combinations of ion-type and activation methods/conditions might provide the structural information of interest [2]. Fragmentation is most useful in addressing questions of bond connectivity or primary structure. For this reason, ion dissociation can be used to differentiate structural (constitutional) isomers, provided they fragment in distinct ways. This is often the case. However, the differentiation of stereoisomers, such as conformational isomers is usually much more difficult via fragmentation. The efforts in this program are directed toward improved means for structural characterization, including both constitutional isomers and stereoisomers. The need for new and improved structural characterization tools in mass spectrometry is driven by the dramatically expanded range of molecules that can now be converted to gaseous ions.

Molecular mass spectrometry currently plays roles in virtually all areas of physical science due in large part to major advancements in means for generating gaseous ions. In particular, the introduction of spray [3,4] and desorption [5,6,7] methods has led to a dramatic increase in the range of molecules amenable to mass spectrometry and tandem mass spectrometry. The development of novel approaches to ionization continues to take place, particularly in the area of so-called 'ambient ionization' [8,9,10,1112,13,14,15,16], which encompasses a wide range of phenomena associated with generating ions external to the mass spectrometer and transporting them to and into the instrument. The introduction and continued development of these ionization methods has generated the need for innovation in instrumentation to address greater demands for mass analysis performance. Improvements in mass range, mass measurement accuracy, and mass resolution, for example, were all motivated by the expansion in the range of gaseous ions that can be generated by the novel ionization methods. Approaches for mass measurement involving time-of-flight (TOF) [17,18] and ion trapping now dominate most molecular mass spectrometry applications. In the latter category, several distinct classes of trapping devices, including electrostatic traps [19,20,21,22,23], electrodynamic traps [24,25,26], and ion cyclotron resonance instruments [27,28], are now in common use. Several of these technologies can provide both mass resolution well in excess of 10,000 FWHM and mass measurement accuracies at the ppm and, in some cases, ppb levels. Electrodynamic multi-pole transmission devices [29], ion funnels [30], and ion carpets [31], are commonly now used as ion transmission devices to maximize ion sampling/transport efficiency. Collectively, these developments have enabled high performance mass measurements to be applied to a wide array of molecules at concentration/quantity levels unheard of a few decades ago.

The advances in ionization have also driven further research into means for ion structural characterization. The most useful approaches apply structural probes on mass-selected ions (i.e., within the context of a tandem mass spectrometry experiment). The most common approach for primary structural characterization for the past forty years in tandem mass spectrometry has involved some form of collision-induced dissociation (CID) [32,33,34,35] involving hyperthermal collisions of ions with gaseous targets. While CID is a powerful and broadly applicable approach, it is not uncommon for CID to fail to provide the structural information of interest for a particular analyte. For this reason, many other activation methods have been developed [36], such as collisions with surfaces (i.e., surface-induced dissociation) [37,38,39], photodissociation using either IR [40,41,42] or UV [43,44,45] radiation, and electron irradiation [46,47,48]. The approaches just mentioned involve the deposition of energy into an ion without directly altering the ion-type. That is, they excite the ions into higher electronic and/or vibrational states that lead to fragmentation. A variety of new approaches for dissociating ions have also been developed

recently that involve altering the ion-type as part of the overall process. An example is the so-called electron-capture dissociation (ECD) technique [49,50], whereby a multiply-charged cation captures an electron with subsequent fragmentation occurring from the charge-reduced species. Analogous processes involving electrons transferred to [51] or from [52,53] multiply charged ions in ion/ion reactions have also been developed. Commercial instruments have become available that are capable of performing these electron transfer experiments and they are now commonly used in proteomics research, for example [54]. Furthermore, collisions of ions with metastable atoms [55,56] and electron detachment from irradiation by fast electrons [57,58] have also been shown to give rise to electron transfer reactions followed by dissociation.

Some of the dissociation methods just mentioned generate odd-electron species from the even-electron ions that are typically generated by the spray and desorption methods. Radical ions, for example, often show fragmentation behavior that is quite distinct from their even-electron counterparts [59,60]. For this reason, a variety of approaches have been explored for generating odd-electron ions from relatively large analyte species either via a gas-phase process [61,62,63] following condensed-phase derivatization or by altering ionization conditions [64,65,66,]. It is widely appreciated that the nature of the gas-phase ion, or ion-type, plays a major role in determining the favored dissociation reactions of an ion and, as a result, the structural information that can be derived. However, the ion-type that provides the structural information of interest may be difficult to generate directly, as is the case with radical peptide cations. This can sometimes be addressed by derivatizing the analyte prior to ionization, as is done with several of the methods devoted to generating peptide radical cations [61-63]. We have found that gas-phase ion/ion reactions can be particularly useful for transforming ions from one type to another. Ion/ion reactions have been carried out at or near atmospheric pressure prior to sampling products into the mass spectrometer [67,68] and within electrodynamic ions traps capable of simultaneous storage of both ion polarites [69,70]. The latter approach provides good temporal and spatial overlap for the ions and has the advantage that both ionic reactants can be mass-selected prior to reaction, which affords the well-known benefits of MS^n. Furthermore, the latter approach provides greater control over ion numbers of each polarity because the 'fill time' for each reactant is controlled independently. Most work with ion/ion reactions, including our own, has focused on either single proton transfer or electron transfer. However, an increasingly wide range of efficient and rapid ion transformations in the gas phase have been demonstrated with ion/ion reactions that go beyond simple proton or electron transfer.[71] For example, we recently demonstrated several ion/ion reaction approaches to transform even-electron multiply-protonated peptides to radical cations in the gas-phase using standard electrospray ionization conditions without recourse to condensed-phase derivatization [72,73]. One demonstrated approach begins with generation of the persulfate anion, $HS_2O_8^-$, via electrospray ionization in the negative mode. CID of this anion generates an abundant sulfate radical anion, $SO_4^{-\bullet}$. This reagent anion reacts with multiply protonated analyte ions via transfer of one proton and one hydrogen atom to yield sulfuric acid and a radical cation of the analyte:

$$[M+nH]^{n+} + SO_4^{-\bullet} \rightarrow [M+(n-2)H]^{+\bullet} + H_2SO_4 \qquad (1)$$

The calculated bond dissociation energy (BDE) for $H\text{-}SO_4^-$ of 454 kJ/mol is significantly greater than that the X-H BDEs in all of the amino acids with the exceptions of the aromatic C-H bonds.[74] Accordingly, we have found that $SO_4^{-\bullet}$ is an efficient and robust reagent for transforming multiply protonated analyte species to radical cations.

Another category of ion transformation involves the introduction of one or more metal ions into a multiply protonated analyte ion. Metal cationized species often undergo distinct fragmentation reactions, particularly when excess protons are absent so that proton catalyzed reactions cannot compete. In an earlier project period in this program, we demonstrated the ability to insert virtually any metal ion into a multiply protonated ion provided a suitable anionic metal-ligand complex can be generated by negative electrospray [75]. We have yet to find a metal salt that does not generate suitable anions via electrospray. For example, negative electrospray of a solution of $Au(III)Cl_3$ yields abundant $Au(I)Cl_2^-$ and $Au(III)Cl_4^-$ anions. Either Au(I) or Au(III) can be switched into a multiply protonated analyte. In the case of Au(I) insertion, the generic reaction for a doubly protonated analyte is:

$$[M+2H]^{2+} + Au(I)Cl_2^- \rightarrow [M+Au(I)]^+ + 2HCl \qquad (2)$$

Metal cationized species also often show quite distinct fragmentation behavior relative to protonated species. In this case, we have shown that gold cationization leads to favored cleavages at disulfide linkages [76,77], in contrast with protonated species, for which disulfide bond cleavage is generally not competitive.

The two ion/ion reaction examples described above are a subset of the gas-phase ion transformations that have been found to be possible with ion/ion reactions that do not rely on single proton or electron transfer. We found in 2009 that functional group selective chemistry could occur with high efficiency (approaching 100% in favorable cases) via ion/ion reactions. We then realized that it would be possible to 'derivatize' mass-selected analyte ions in the mass spectrometer for structural characterization on the tens to hundreds of milliseconds time-scale. This capability would lead to a significant expansion in the range of ion-type transformations that could be effected and would avoid complications associated with mixing reagents in solution with the analytes of interest. The recent advances in rapid and selective covalent reactions in analytical mass spectrometry are significantly expanding the specificity of mass spectrometry in characterizing ion structures. They have opened up altogether new lines of research in gas-phase ion chemistry will clear implications for molecular analysis.

III. Summary of Major Thrusts of this Research Effort

This progress report narrative provides a high level summary of the roughly 15 year period since the PI moved to Purdue. OBES funding began on September 01, 2001 and ended on May 31, 2016. Most of the effort over this period was devoted understanding and developing the physics and chemistry that takes place in electrodynamic ion traps and fundamental aspects of ion/ion chemistry. Electrodynamic ion traps were first introduced to the analytical mass spectrometry community in the mid-1980s as stand-alone low-resolution mass spectrometers. They have since become commonplace as storage devices, reaction vessels, and ion processing devices either as stand-alone instruments or as components of instruments that combine various technologies. Much of the work has focused on ion traps as reaction vessels and as means for activating ions for the purpose of structural characterization. Figures 1 and 2 provide a high level perspective. Figure 1 is intended to convey that primary structural information in tandem mass spectrometry is strongly dependent on both the ion-type and the dissociation method. Considerable effort over the years has been directed to the study of various means for dissociating ions in electrodynamic ion traps. This effort relates to the acronyms in the beaker on the right. In

particular, this effort has played a major role in developing the understanding of collisional activation in ion traps under a variety of conditions both via modelling and experiment. This has involved the use of ion acceleration techniques that employ either supplementary AC or DC fields.

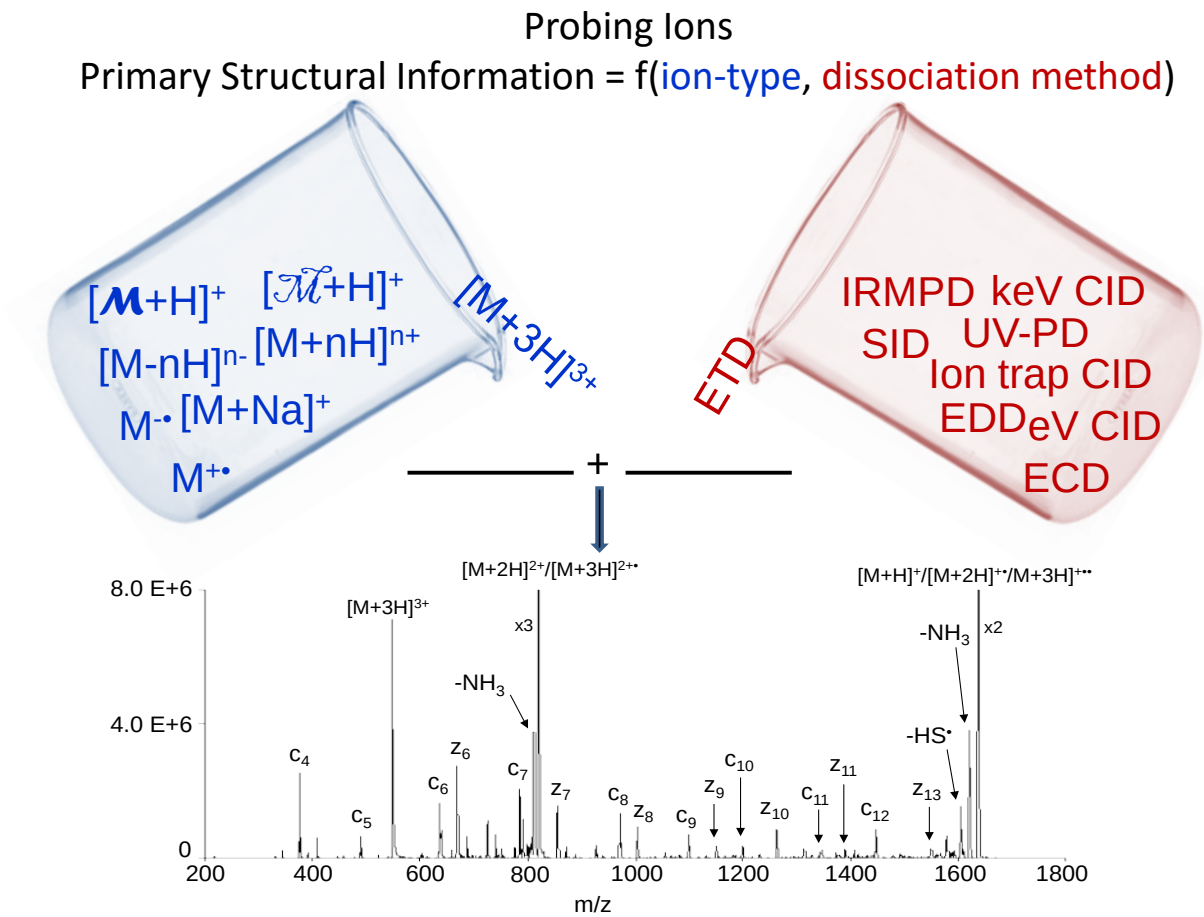

Figure 1 – Schematic depiction of the importance of the combination of ion type with dissociation method in determining the structural information that can be obtained in a tandem mass spectrometry experiment.

A major area if effort in this program since 1995 has been the study of the reactions of multiply-charged ions with ions of opposite polarity. The introduction of electrospray ionization enabled the creation of this field because at least one of the reactants could be formed with multiple charges so that at least one of the reactants retains a net charge. The PI was in a good position to capitalize on this opportunity because electrodynamic ion traps are capable of storing ions of opposite polarity simultaneously and in the same location. The PI and co-workers therefore used electrodynamic ion traps as reaction vessels to both discover and develop ion/ion reactions. It has since become clear that ion/ion reactions are uniquely powerful as means for converting ions from one type to another. This has enabled new types of ion transformations to enhance the structural characterization capabilities of tandem mass spectrometry. Hence, ion/ion chemistry relates to the left beaker of Figure 1. Various nominal ion-types are depicted in Figure 2. Over the course of this project, reactions that can make all of the depicted transformations and many more have been

discovered and studied. Reactions (1) and (2) are generic reaction types among dozens discovered and studied in the course of this research. Together, the work with dissociation methods and ion transformation chemistries has led to a major expansion in the capabilities of tandem mass spectrometry for ion structural characterization.

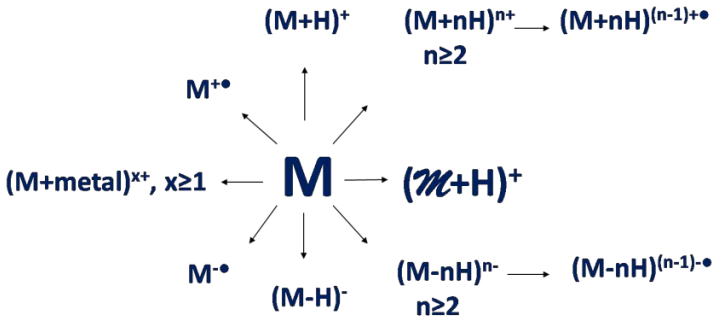

Figure 2 – Depiction of common ion-types that can be generated from a molecule (M) of interest. The $\mathcal{M}$ species represents a covalently modified form of M. Reagent ions have already been identified that can transform most of the ion types listed to other ion-types, including many not shown schematically.

In the final budget period, in addition to continuing our work with ion/ion chemistry, we a new initiative with a collaborator, Prof. Tim Zwier, on cold-ion spectroscopy was begun. This effort entails the acquisition of the UV and IR spectra of mass-selected polyatomic ions cooled to roughly 10 K. This is an exciting line of work because it provides a new dimension to the structural characterization of polyatomic ions. The ability to probe the ions spectroscopically provides a powerful approach to probe higher order ion structure that goes beyond the bond-connectivity information available from ion fragmentation. Within the context of this effort's historical emphasis on structural characterization, the ion spectroscopy work represents an exciting new possibility for expanding the power of tandem mass spectrometry.

IV. Impact and Highlights

Mass spectrometry, both elemental and molecular, has been a longstanding impact area for the Separations and Analysis Program. In fact, this program has impacted no other analysis area more than it has impacted analytical mass spectrometry. An important indicator of impact for this program is the number of national and international awards garnered by the mass spectrometry researchers within the program. For example, the major national award for career contributions to mass spectrometry is the ACS Field and Franklin Award, which has been awarded to Graham Cooks (1991), Jean Futrell (2007), Scott McLuckey (2012), and David Russell (2013). The major award granted by the American Society for Mass Spectrometry (ASMS) is the Distinguished Contribution Award, which is focused on a singular achievement, as opposed to career achievement. This award has been granted to Cooks (2006) and McLuckey (2016). The major international mass spectrometry award, the Thomson Medal, is granted by the International Mass Spectrometry Foundation (IMSF) and has been awarded to Cooks (1985) and McLuckey (2016). The major national mid-career award in mass spectrometry is awarded by the ASMS in the form of the Biemann Medal. McLuckey was the first recipient of this award (1997), which has subsequently been granted to Gary Van Berkel (2005) and Julia Laskin (2008). The major mid-career international award, the Brunnée Award, is granted by the IMSF and was awarded to McLuckey (2000). All of these awards are highly competitive as there are in excess of 7500 ASMS members and 40+ national affiliate societies in the IMSF. The folks working in the area of elemental mass spectrometry, such as Sam Houk, Gary Hieftje, etc. have also garnered many

national and international awards in the atomic spectroscopy community, which is where much of the elemental MS work is focused.

The recognition that has come to this research program began in 1997 with the inaugural Biemann Medal, which was given for our pioneering work in the unimolecular dissociation and ion/molecule reactions of multiply-charged ions. The Nobel Prize winning work of John Fenn for the development of electrospray ionization opened up new research areas and we were among the first to study the fundamental role that multiple charging plays on the unimolecular and bimolecular reactions of these novel ions. Today, of course, multiply charged ions are commonplace and much of what was learned in this project with OBES support is now part of the knowledge base passed on to newcomers to the field. In 2000, the Curt Brunnée Award was granted to the PI for work with electrodynamic ions traps. Understanding the chemistry and physics of such traps has been a major objective of the PI for many years. The next major recognition came in 2007 with the ACS Award in Chemical Instrumentation, which reflected both the PI's original work with ion traps as well as the work performed in the new century, much of which was supported by the OBES. In 2012, the PI was awarded the ACS Field and Franklin Award, which acknowledged both ion chemistry and instrumentation work. This past June, the PI was awarded the ASMS Distinguished Contribution Award for ion/ion chemistry. This line of work was initiated under OBES support and has been an area of fundamental investigation for the PI and his students ever since. The PI and his group are widely recognized as the pioneers of this area and OBES deserves much of the credit for the initiation and development of this field. Ion/ion reactions are now available on many commercial instruments and their application will grow substantially in the coming years. In August of 2016, the PI received the Thomson Medal from the IMSF, which acknowledges both research and service to the MS community. Examples of the latter have been the PI's longstanding editorship of the International Journal of Mass Spectrometry and his service as ASMS Present, Vice-President for programs, and Past-President. Other national and international recognitions that can also be credited to OBES sponsored work include the 2008 ANACHEM Award from The Association of Analytical Chemists and the 2012 Theophilus Redwood Award in Analytical Chemistry from the Royal Society of Chemistry.

Finally, and perhaps most importantly, the OBES support has played an essential role in the education and training of several dozen Ph.D. students and post-docs. These young aspiring scientists are responsible for much of the work that is recognized by the awards mentioned above. This list of awards that the students and post-docs have earned over this period is truly impressive. In the 16 years that the PI has been a faculty person at Purdue, students from his group have won the Mellon Award, which goes to the top analytical graduate student in Purdue's roughly 130 student analytical chemistry program, seven times. They have won too many travel and poster awards to track and several have gone on to faculty positions themselves. The collective impact of these scientists will be enormous.

The following papers acknowledging OBES support have been either published or accepted since the inception of this project at Purdue University in 2001:

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Bu, J.; Fisher, C.M.; Gilbert, J.D.; Prentice, B.M.; McLuckey, S.A. *J. Am. Soc. Mass Spectrom.* **2016**, *27*, 1089-1098. "Selective Covalent Chemistry via Gas-Phase Ion/ion Reactions: An Exploration of the Energy Surfaces Associated with N-Hydroxysuccinimide Ester Reagents and Primary Amines and Guanidine Groups."

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