Development of tandem mass spectrometry: one perspective

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Abstract

The historical roots of tandem mass spectrometry or MS/MS (an invaluable tool for determining molecular structure and mixture analysis) are reviewed from the perspective of an active participant. The driving force for creating the first (and only) five-sector tandem mass spectrometer in the period 1962–1965 was to establish mechanisms of low energy ion–molecule reactions unequivocally and to evaluate the dependence of these reactions on ion kinetic energy. The invention and deployment of several other specialized instruments in the 1970s (drift cell and tandem ion cyclotron resonance spectrometers, hybrid tandems, and triple quadrupole instruments) also had fundamental studies of ion reactions as the research objective. The focus on low energy ion chemistry has evolved into collisional activation, the basis of analytical applications of MS/MS, as a natural evolution of scientific interest. The first such studies utilizing a crossed-beam hybrid MS/MS addressed single collision gas phase activation and has recently been extended to surface collision activation. The important parallel development of these methods and the metamorphosis of MS/MS from a suite of research tools into analytical practice using commercial instrumentation are discussed briefly. (Int J Mass Spectrom 200 (2000) 495–508) © 2000 Elsevier Science B.V.

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1. Introduction

Tandem mass spectrometry is the branch of mass spectrometry concerned with selection of a particular ion (a component of the normal mass spectrum) formed from a molecule or a mixture of molecules and its activation, usually by one or more collisions, to generate characteristic secondary fragment ions. The motivation may be analytical, determination of ion structure(s), fundamental studies of properties of ions, or any combination thereof. The study of unimolecular (metastable) decay of mass selected ions with sufficient internal energy to dissociate spontane- ously in field-free regions of the mass spectrometer is a subset of tandem mass spectrometry. When single (or a few) collisions with a neutral gas are employed the technique is called collision-induced dissociation (CID) or collision-activated dissociation and is called surface-induced dissociation (SID) if a solid is used for the activation of the ion. In the collision process a fraction of the ion's kinetic energy is transferred into internal energy, effecting its dissociation into various fragment ions; the extent of fragmentation depends upon the total internal energy content of the excited ion. This simple methodology, commonly used and commercially available on most instruments, has been successfully extended to characterize high mass complex molecules and mixtures even though the underlying phenomena for complex ions are not fully

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understood [1]. By now the instrumentation for tandem mass spectrometry is quite sophisticated and well known. Neither the technique nor its implementations are the subject of this article. Rather, this article describes, from the viewpoint of an active participant, some of the ancestors of present day instrumentation developed over the past 40 years.

Applying tandem mass spectrometry to fundamental science problems and creating unique instruments for this purpose has been a central theme of my career in mass spectrometry. These wanderings over the scientific landscape were strongly influenced by the evolving interests and talents of my research group, primarily at two academic institutions. This invited article is not intended to be a comprehensive review of tandem mass spectrometry and important contributions by other researchers will inevitably be overlooked. Rather, the intent is to describe from a very personal perspective the evolution over time of tandem mass spectrometry as it metamorphosed from a research tool for investigating ion–molecule chemistry and physics into a valuable methodology for addressing the most demanding analytical challenges of the day. An additional objective is to provide an eye-witness account to the current generation of mass spectrometrists to give them the flavor of how the field developed.

When I was a graduate student at the University of California at Berkeley, mass spectrometry had barely penetrated into academe. My thesis research was in radiation chemistry and I was intrigued by two topics in ion chemistry that emerged concurrently. One was the extension of absolute rate theory by Wahrhaftig, Eyring, Wallenstein, and Rosenstock to mass spectrometry, explaining how internally excited molecular ions evolve in isolation into characteristic fragmentation patterns of mass spectra. The second was papers by Gioumousis and Stevenson pointing out that ion–molecule reactions occur at essentially their collision rate. It was obvious that both developments were relevant to radiation chemistry and that gas-phase radiation chemistry would likely be dominated by ion chemistry. My first publication as an independent scientist was "theoretical" in that I used this hypothesis to calculate the radiolysis yields and distributions

of products for irradiated normal hexane vapor that matched published experimental values within several percent. Since mass spectrometry was obviously the technique of choice for investigating ion–molecule reactions this exercise defined for me the goal of acquiring what was then considered an outrageously expensive instrument.

A few months after leaving Berkeley (in this Cold War era) I was called to active duty as an officer in the United States Air Force and stationed at Wright-Patterson Air Force Base as a research scientist assigned to the Aerospace Research Laboratory (ARL). What seemed at the time to be an interruption to my career proved to be an enormous boost in developing an independent research program involving both analytical mass spectrometry and ion–molecule chemistry. Although I knew nothing about mass spectrometry, ARL authorized me in my second year of military service to purchase a commercial Consolidated Electrodynamics Corporation (CEC) 21-103 mass spectrometer, a modest resolution 180° sector (Dempster type) instrument. Acquisition or access to a mass spectrometer was the necessary and sufficient condition to join the American Society for Testing Materials Committee E-14 (Mass Spectrometry) which was the forerunner of The American Society for Mass Spectrometry (ASMS). This was and is an especially important meeting ground for beginning mass spectrometrists.

2. First five-sector tandem mass spectrometer

My first key co-workers at Wright-Patterson were staff members Dean Miller and Tom Tiernan, along with postdoctoral Fellows Keith Ryan, Fred Abramson and (the late) Lieutenant Wayne Sieck. The latter four colleagues are well known within the mass spectrometry community. However, in many ways research technician Dean Miller was the key player as we invaded the field of mass spectrometry. As a talented electronics specialist he played an absolutely critical role in the modification of commercial instruments to convert them (reversibly) from analytical instruments to tools for investigating ion–molecule
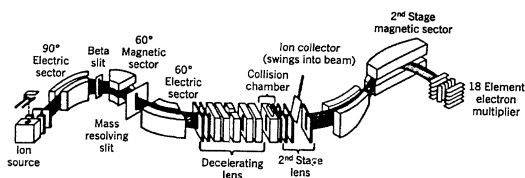
Fig. 1. 1964 five-sector tandem mass spectrometer.

reaction kinetics. He was also responsible for innovative design of circuits and was my assistant in redesign and final assembly of the most sophisticated tandem mass spectrometer developed in the 1960s. He was my only co-author on the first publication describing this instrument, shown schematically in Fig. 1 [2].

Some idea of the technical "leap forward" which this instrument represented can be gained by comparing it to contemporaneous tandems also constructed for the purpose of investigating fundamental aspects of ionization phenomena and ion–molecule chemistry. Probably best known is Lindholm's famous double Dempster mass spectrometer, in which the reactant ion beam crosses at right angles the extraction axis of a collision cell that comprises the ion source of the second stage analyzer [3]. The primary ion beam crossed the chamber at relatively high kinetic energy (typically 50–500 eV) and only thermal velocity secondary ions resulting from charge exchange were extracted and analyzed with high efficiency by the second stage instrument. The tandem instrument developed contemporaneously by Clayton Giese and graduate student Bill Maier at the University of Chicago was the first tandem designed for studying low energy momentum exchange or ion–molecule reactions [4]. The tandem instrument replaced the ion source of a magnetic sector instrument with a 1 in. radius mass analyzer, deceleration lens, and collision cell—a far cry from the technological challenges surmounted in constructing the Fig. 1 apparatus.

Although capable of building substantial parts of airplanes, the machine shops at Wright Patterson were unsuitable for precision machining of a sophisticated mass spectrometer. Accordingly we contracted the task of combining two double-focusing instruments separated by a collision chamber to Consolidated Electrodynamics Corporation (CEC). In 1962 CEC was the leading U.S. manufacturer of analytical mass spectrometers. The top of their line was the CEC 21-110 double-focusing mass spectrometer, a Mattauch-Herzog geometry instrument having both photoplate and electron multiplier detectors. We chose this instrument, or rather off-the-shelf components of this instrument, as our second stage ion detector. Having neither expert knowledge nor prejudice as to intrinsic optical characteristics of Mattauch-Herzog versus Nier-Johnson geometry, and having chosen the former as the ion detector we chose the latter design for the first stage, or ion-gun, mass spectrometer. (This proved to be a particularly good choice in that the beta slit of this geometry instrument sets the band pass of the electric sector, enabling us to define the ion kinetic energy and energy width precisely.) In order to package the tandem instrument more efficiently, CEC included a third electric sector as a steering element to give the tandem spectrometer a relatively compact rectangular footprint. These design considerations established the layout and basic design for the tandem. These issues were worked out with CEC engineers Charles Robinson and (the late) George Parsons. My visits to Pasadena to meet with them and their staff during the construction of the tandem (Fig. 1) were great tutorial experiences on the theory and practice of mass spectrometry.

As noted, the second stage instrument was identical to the CEC 21-110 mass spectrometer. All the other optical components of the spectrometer required design, testing as a prototype and fabrication. An important objective for studying ion–molecule reactions was to reduce ion energy as close as possible to thermal. Our goal was 1 eV, a significant challenge since 10 eV was considered at that time the lowest energy that could be achieved by decelerating ions after mass analysis. Consequently, the first tests on the prototype in Pasadena focused on evaluating the transmission of the reduced-scale Nier- Johnson geometry instrument as a function of accelerating voltage. Essentially flat ion transmission above 100 eV led to the design decision to operate the Nier-Johnson ion gun instrument at 169 V—much lower than the

typical accelerating voltage of several kilovolts. Our initial expectation (and fondest hope) was that dropping the accelerating voltage by a factor of 10 would also reduce, by a factor of 10, the lower limit of ion energy at the collision cell.

This low accelerating voltage also simplified, to some extent, the question of defining instrument ground. This is a vexing problem in all tandem mass spectrometers for which any stage is operated significantly off ground potential. If the final detector is chosen as ground, as in our design, the entire three sector first stage floats at the accelerating voltage of the second stage instrument. In turn, the ion source is offset from ground (the flight tube) by the sum of the first stage and second stage accelerating voltages. In the Fig. 1 instrument the flight tube of the first stage instrument is mounted on ceramic spacers inside the vacuum chamber, which rest on the outer, grounded tube. Offsetting the ion source by an additional 169 V is a relatively simple solution to the voltage isolation problem.

When this impressive instrument was delivered to our laboratory in 1964, we eagerly set out to demonstrate its capabilities. In brief, we wished to mass select a reagent ion, decelerate to the desired final energy, react with a neutral gas at known pressure and path length, and identify secondary ions generated by low energy ion–molecule reactions. It appeared that the capability to scan collision energy to delineate how mechanisms and rate coefficients depended on ion–neutral collision energy was in our hands. We also anticipated that crude determinations of angular dependence would be possible by mounting a second collision chamber at the focal point of the turning electric sector upstream of the collision chamber shown in Fig. 1.

These hopes were dashed by the failure of the instrument, as delivered, to transmit any ions at all when the primary beam was decelerated below 10 eV. Seemingly, the folklore that this was the lower limit for deceleration lenses had been confirmed. Although other group members were mainly engaged in doing some very nice science on a modified CEC 21-103 instrument, Dean Miller and I studied books on ion optics and carried out "design" studies using the

"analog computer" technologies of the day. There were two main analog approaches to ion optics available in this pre-PC era. (Of course, we would have been delighted to have SIMION 6.0; however, in 1965 computers were located in buildings, not on desktops.) The more elaborate approach (and more fun until we were tired of it) involved stretching several square feet of thin rubber sheet between blocks to simulate potential fields and rolling marbles on this surface while one of us moved the blocks up and down to simulate adjustment of lens potentials. Among other things the series of experiments supported our experimental observation that no ions would be transmitted by the original lens configuration. In short, trajectories became scrambled and no marbles got through the slot when the blocks were elevated above a certain level. The second and more useful approach (used by us for more than a decade) involved drawing possible lens designs in silver paint on graphite-coated paper, applying battery voltages to the "lens plates" and measuring the equipotential field lines with a voltmeter. Plotting (by hand) these equipotential field lines provided important clues but little predictive knowledge about ion optics designs and acceleration fields.

These crude experiments gave us the courage to fabricate some possible lens designs, mainly variations of lens configurations we found in electron optics books and mocked up in our "analog" models. The end point of this study was rather discouraging; we concluded that in the geometric space available no existing lens design would allow us to decelerate the ions to 1 eV and reaccelerate them to 3 keV (while maintaining tight focus of ion beam trajectories in both the collision chamber and second stage analyzer). In other words, to achieve our goal it appeared that we had to redesign the vacuum chamber and all the optics between the two mass analyzers.

There were side benefits in our painful experience with self-taught ion optics. We discovered, but did not pursue, the phenomenon of SID when ions were deflected onto the walls of the three electric sectors in the Fig. 1 instrument. We also learned that one of the effects of the relatively low voltage for the first stage spectrometer was space charge defocusing of the

beam when we ran high ionizing electron current in the electron impact source (as we usually did). This was remedied by adding two Einzel lenses to the electric sector entrance and exit plates [5]. Adjusting these lenses, which were tied together electrically, shifted the focal points of the sector to compensate for the larger opening angle of the beam caused by coulomb repulsion. We also learned to make our own ion sources and learned the benefits of relatively open ion optics to keep ions far enough away from electrodes that their trajectories more closely resembled textbook examples. These lessons were pragmatically useful in many future projects.

Certainly the most significant byproduct of our excursion into charged particle optics was development of the technique of decoupling the electric sector and accelerating voltage of either/both of our double focusing instruments to enable the investigation of metastable ions [6]. Because ions which decay unimolecularly in the field-free region between the electric and magnetic sectors continue in flight with the same velocity as the primary ion, it can easily be shown that the accelerating voltage which transmits these ions through the electric sector (at the same kinetic energy as normal ions) is given by

$$E_m = m_p/m_s \times E_0 \qquad (1)$$

where E_0 is the accelerating voltage which generates the normal mass spectrum and m_p and m_s are the masses of the primary and secondary ions, respectively . This enables the isolation and precise identification of metastable ions (plus ions generated by background gas CID) and was the basis for the first implementation of tandem mass spectrometry in commercial instruments.

Interestingly, Keith Jennings was a summer visitor in our research group and we learned, shortly after his arrival, that he had independently developed the same metastable defocusing or decoupling technique in Great Britain. After we had exchanged preprints of two manuscripts, which were already in press, we agreed that Keith would investigate that summer metastable decomposition of the α,α,α-trifluoro toluene molecular ion [7]. This utilized the second stage

of our tandem where we were continuing our frustrating pursuit of an optical solution to the ion deceleration problem. An interesting sidebar is that this compound is one of the most noxious lacrymators ever found in a normal chemical storeroom. A few drops evaporating in our fume hood led to the emergency evacuation of the Aerospace Research Laboratory and to the discovery that the exhaust vent from the fume hood in my laboratory pointed directly toward the main air intake of the HVAC system.

When we were satisfied that we could not find a solution to our optics problem based on our own knowledge and extant literature, I visited experts at the National Bureau of Standards (the precursor to NIST) where I presented the problem to Chris Kuyatt and J. Arol Simpson in the Electron Optics Section. Within a few hours they proposed a solution that we later described as a "slot" lens (e.g. a slit lens which is long in the direction of travel). Fig. 1 includes a rather distorted view of the slot lens, which is actually 3 cm long. The important feature of the slot lens is that it has a thickness sufficient to produce two field gradient regions per element. The focusing power of such a lens, which has subsequently become a standard lens in charged particle optics and is correctly described as a rectangular tube lens, was assumed to be twice that of a slit lens of similar dimensions. This design enabled the deceleration and re-acceleration in roughly half the linear space required for these functions by conventional slit lenses.

Constructed according to these simple principles, this lens worked remarkably well and has been used by us, and others, in subsequent tandem designs. Years later, it was amusing to compare the semiempirical design worked out in a one day visit to NBS with an accurate computer solution of LaPlace's equation for a rectangular tube lens. The correspondence between modern knowledge and early empiricism is close. In any event it worked extremely well, better than Kuyatt and Simpson expected. Designed to decelerate ions to 1 eV, it actually had a principal focus at 0.7 eV. Since the cross section for ion–molecule reactions following the Langevin equation has an inverse dependence on velocity, the relative intensity of secondary ions maximized around 0.3 eV,

enabling the straightforward investigation of energy dependence of ion–neutral collisions from 0.3 eV to tens of electron volts with the Fig. 1 instrument. Good luck and persistence paid off handsomely.

Once this breakthrough was achieved we had the research tool to investigate a number of intriguing aspects of ion–molecule chemistry and physics [8–22]. The first experiments clarified kinetic, or ballistic, isotope effects manifested in the kinetic energy dependence of proton transfer reactions. A "normal" isotope effect was observed at the low energy limit of about 0.3 eV. With increasing energy the mechanism goes over to a "proton-stripping" reaction which deposits internal energy into the new bond formed in the product. The greater momentum in deuteron transfer versus proton transfer leads to dissociation of the deuterated product at a lower kinetic energy than the reference proton transfer reaction and the apparent isotope effect goes to infinity. The characteristic energy for this transition can be estimated from such a ballistic model and our experiments demonstrated that the prediction was approximately correct. We found the general rule that rate coefficients for condensation reactions fall off very rapidly with increasing collision energy and that hydride transfer reactions fall off less rapidly and that proton transfer reactions persist to rather high energies. Exothermic electron transfer reactions often exhibit very large rates at low velocity and decline to a lower but high value above a few eV. This is readily explained as proceeding via long-range electron transfer (rectilinear trajectories) at energies greater than a few electron volts, augmented by an orbiting complex (Langevin) mechanism at low energy. We investigated ion–molecule chain reactions one step at a time, demonstrated effects of ion structure on reactivity, collisional stabilization as an essential step in chain polymerization reactions, and gas phase alkylation of benzene.

A great opportunity that we considered, but did not pursue with the Fig. 1 instrument, was potential analytical applications for the tandem mass spectrometry. The fact that secondary ion intensity was so low in comparison with detected ion currents from a single stage double focusing spectrometer, particu-

larly at higher ion energy where collision-induced reactions predominated, that we concluded such a complex instrument would not be useful for analytical purposes. What we ignored was the fact that "chemical noise" in the complex optical path of the tandem experiment was suppressed by many more orders of magnitude than signal. This fact, coupled with the very high gain of electron multiplier ion detectors, makes multiple sector tandem mass spectrometers very useful for structure elucidation and other analytical applications—as later demonstrated in several laboratories. Leaders of this thrust of tandem mass spectrometry include Graham Cooks, Fred McLafferty, and Keith Jennings, among others. Fundamental studies of high-energy collision phenomena, vigorously pursued by Cooks, John Beynon and others, were also obviously accessible to the Fig. 1 instrument but ignored by the inventors.

3. Tandem ion cyclotron resonance

The impact of this elegant research tool on our understanding of low energy ion–molecule reactions would have been more profound but for the coincidence that Peter Llewelyn of Varian Associates introduced the competing technique of ion cyclotron resonance (ICR) as a commercial product in the same time frame. Vigorously pursued by John Baldeschweiler and his brilliant cadre of students (and their progeny), who became leading savants in the field of low energy ion chemistry, ICR emerged in the late 1960s as the technique of choice for the kinds of problems we addressed using the Fig. 1 tandem mass spectrometer. I joined the ICR parade when I began my academic career at the University of Utah in 1967.

Although my timing in "inventing" tandem mass spectrometry contemporaneously with ICR was unfortunate, my timing in entering academe was perfect. 1967 was the year that per capita research funding of science faculty in universities peaked, and it was relatively easy, without setup funds, to fund the purchase of three mass spectrometers. One of these was a Varian Syrotron® ICR spectrometer. Since I had several unorthodox experiments in mind at the
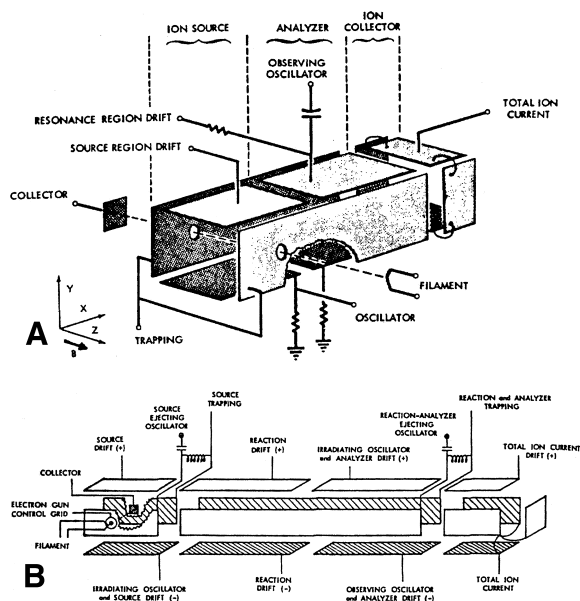
Fig. 2. (a) Varian syrotron drift cell and (b) Utah drift cell tandem ICR spectrometer.

outset my Varian spectrometer was mounted in a 12-inch electromagnet rather than the standard 9 in. magnet. The arrival of this wonder in my Salt Lake City laboratory was a bittersweet experience; it was shipped under vacuum from Palo Alto and operated perfectly its first full day in residence. This stands in stark contrast to our experience with the Fig. 1 instrument.

Building your own (or drastically modifying the commercial product) nevertheless emerged in my research group at Utah and has survived as a central theme over the years. It is more painful than buying a new widget but has the singular merit that you understand both the quirks and capabilities of the homemade device rather better. Consistent with this philosophy, we significantly modified the Varian ICR cell within a few months, relying in part on what we had learned about ion optics in building the five-sector tandem. Fig. 2 compares the "as-delivered" Syrotron® drift cell with the Utah drift cell, which we consider the first serious implementation of "tandem-in-space" ICR. Prior to Marshall and Commisarrow's invention of Fourier transform ICR, drift cell ICR involved the generation of ions by electron impact and transfer of

those ions into the detector region, both within the uniform magnetic field of the electromagnet. Drift velocity was controlled by imposing a weak electric field at right angles to the magnetic field.

Ion drift velocity perpendicular to both fields is readily calculated from the vector product

$$V = E \times B \qquad (2)$$

where E is the electric field strength perpendicular to the magnetic field and B is magnetic field strength.

In the Syrotron® spectrometer, unchanged primary ions and secondary ions were migrated into the detector section and recorded as either differential or integral signals by a marginal oscillator, in direct analog to contemporary nuclear magnetic resonance technology. The final section in the Syrotron® cell shown in Fig. 2(a) is a set of plates connected to an electrometer which monitors total ion current.

Fig. 2(b) adds an additional section which was very useful in working out ion–molecule reaction mechanisms and effects of ion kinetic energy on reactivity. This reaction section separates the ion source reaction and detection steps and enables the investigation of kinetic energy dependence of reaction rates. Relatively strong E fields in the source and detector combined with a weak E field in the reaction zone both spatially separated ion formation, reaction and product detection and ensured that most of the reaction occurred before ions were energized in the detection step. Timed ejection pulses on isolated trapping plates permitted us to measure the times spent in each section and enabled measurement of accurate rate constants. Mechanisms were unambiguously established by monitoring the decline in intensities of secondary ions while applying variable frequency rf in the source region at high-enough amplitude to eject reagent ions at their resonant frequency. For more sensitive interrogation, the difference signal could be generated by modulating the marginal oscillator phase sensitive detector. The electrometer signal was used to calibrate absolute sensitivity of the marginal oscillator. Finally, by energizing ions in the "selector" section at their resonant frequency and turning it off at a predetermined time, we could place
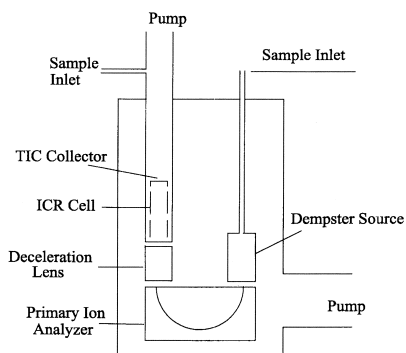
Fig. 3. 1974 tandem ICR mass spectrometer.

Fig. 4. 1974 crossed-beam tandem apparatus.

ions in parking orbits of defined kinetic energy and investigate dependence of rates on ion kinetic energy.

From the perspective of sophisticated "tandem-in-time" Fourier transform ICR these drift cell ICR experiments now appear rather crude. However, the reader is reminded that the development of FTICR required fast and sophisticated computers scarcely dreamed of in the Syrotron® era.

Although drift cell ICR was obviously a very powerful method for investigating ion–molecule re-actions—especially, in our view, using the Fig. 2(b) cell—there were many circumstances in which the reagent ion selection capability of a multiple-sector tandem provided clear advantages. Accordingly we acquired a second 12 in. electromagnet at Utah and constructed the tandem ICR shown in Fig. 3. My principal collaborator in this endeavor was Postdoc-toral Fellow David Lee Smith. In the Fig. 3 instrument a miniature Dempster 180° sector mass analyzer within the uniform field of the electromagnet is the mass sector for the ICR second stage mass analyzer. The tightly enclosed ion source section included split repellers that corrected for the displacement in ion trajectories caused by the high magnetic field. The enclosed source permitted us to increase the pressure in the source and use ion–molecule product ions as reactants in the ICR analyzer section. One of the nice properties of the 180° sectors is a plane of symmetry at 90° that implies ion trajectories entering and leaving the sector are identical. Accordingly identical sets of asymmetric potential lenses served as acceler-ation and deceleration lenses. The final element was a
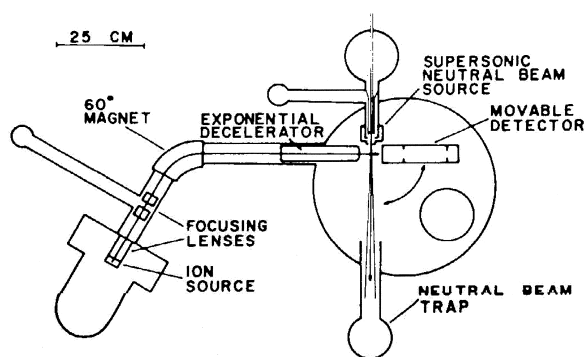
pair of closely spaced plates in the deceleration lens, which comprise an energy filter. Only ions with cyclotron orbits small enough to pass through this slot can enter the ICR cell.

In this way we implemented in the very small space within the pole pieces of a 12 in. electromagnet the main features of the original Fig. 1 tandem spectrometer. In particular a moderate resolution mass selector ion gun and an energy selector comprise the first stage of the tandem. The second stage was a relatively high-resolution mass analyzer with the added flexibility of standard drift cell ICR experi-ments. It had the singular advantage that the starting point of our ion molecular chemistry studies was less than 0.2 eV translational energy. Using the Figs. 2 and 3 research tools we learned a lot about ion–molecule reactions and mechanisms, including explicitly many of the effects of ion internal energy and translational energy on reactivity [23–53].

4. Hybrids and quadrupoles

The missing information for characterizing the dynamics of ion–neutral collisions in the tandem instruments already described was quantitative infor-mation on how cross sections for these reactions depended on scattering angle and kinetic energy-so-called double differential cross sections. Accordingly the next tandem mass spectrometer in our repertoire was the crossed-beam device shown schematically in Fig. 4. Although it used a magnetic sector mass

selector and a quadrupole secondary ion analyzer, we consider it a very early example of a hybrid tandem mass spectrometer.

Key collaborators in designing and constructing this instrument were postdoctoral Fellow Calvin Blakeley and graduate student Marvin Vestal [54]. (Although technically Marvin was a graduate student he was already an established scientist and a full partner in this project.) We were inspired by Professor Yuan Lee's success in creating the first truly successful supersonic jet molecular beam apparatus and honored him by creating a one-third scale version of his neutral jet design for our ion–neutral crossed-beam apparatus. The dimensions for our neutral supersonic beam apparatus were obtained using a micrometer to take measurements from a figure in Lee's first publication on this topic [55].

Th magnetic sector was salvaged from an obsolete Hitachi mass spectrometer (gifted to the University by the Perkin Elmer Corporation) and the quadrupole mass filter was an obsolete unit gifted to us by the Finnigan Corporation. The main vacuum chamber was a standard glass bell jar, which was a great advantage for observing sparks from discharges and electrodes which had dropped off when the entire stage was rotated via a mechanical feed-through. However the insulating qualities of glass required such things as transparent mesh, aquadag paint and other trickery to eliminate surface charges and enable the detection of nearly thermal energy ions.

The most important design feature introduced by Marvin and Cal in the Fig. 4 apparatus was an exponential deceleration lens with the special property of keeping the beam nearly parallel as it was decelerated to low energy. The fabrication of this device tested the patience and soldering skills of graduate student Phil Ryan. Another important feature was the high-resolution energy analyzer, which proved capable, in some cases, of resolving vibrational populations of diatomic product ions. New methods of signal processing using ion counting techniques also entered our repertoire. Weak signals from the encounter of the ion and neutral beams at the crossing point are pulled out of background noise counts by adding counts to a registry when the chopper is open and subtracting counts when the chopper is closed. By this time, using at least a crude computer (initially a multichannel scaler and later a PC) to accumulate counts, do simple data conversions, and keep track of experimental parameters was an essential feature of this class of experiments.

A seemingly mundane feature, which proved to be quite important, is the beam dump on the opposite side of the vacuum chamber from the supersonic jet. The 1 mm diameter jet expands to about 1 cm in crossing the chamber and an apertured diffusion pump removes nearly all the neutral gas when the system is properly aligned. Random noise counts are suppressed by more than one order of magnitude if the pressure in the main chamber does not change between "chopper open" and "chopper closed." Further, the ratio between the pressure for chopper open versus chopper closed read on an ion gauge mounted in the line-of-sight beam dump became the most important metric for alignment and performance of the supersonic jet.

For nearly 30 years the Fig. 4 apparatus has been one of only two such ion–neutral crossed-beam apparatuses capable of detecting very low kinetic energy product ions and defining their angular scattering characteristics. The other apparatus is in Zdenek Herman's laboratory in Prague, Czech Republic, where he and his students continue to define important dynamics features of ion–neutral collisions. Distinguishing features of the Fig. 4 apparatus are higher resolution mass, energy and angular analyzers. In particular, our combination of a very effective lens for decelerating ions to low energy, a high transmission energy analyzer capable of transmitting very low energy ions to the quadrupole mass analyzer and an efficient supersonic jet neutral beam enabled the measurement of ion–molecule reaction dynamics at very low relative energies.

As noted, the Fig. 4 instrument has the unique capability to characterize charge transfer reaction dynamics. This requires the detection of low velocity ions after electron exchange of neutrals with high velocity ions. Since momentum transfer associated with the transferred electron is trivial the product ions have the velocity of the original neutral species. The

"trick" is to operate the supersonic jet in a seeded gas expansion mode with hydrogen or helium as the driver gas so that the neutral beam actually has velocity comparable to that of the decelerated reactant ion beam. The combination of the supersonic jet neutral beam and the exponential deceleration lens uniquely qualify the Fig. 4 instrument for this class of experiments.

Key features of ion–molecule reaction dynamics, which were established using this apparatus, included issues such as isotope effects, formation of persistent complexes at low relative velocity (confirming the Langevin mechanism), dynamics of stripping reactions, and their dependence on collision energy [56–71]. Scattering resonances in charge transfer (explicitly the definition of narrow windows of kinetic energy for mechanisms to open and close) were among the most interesting discoveries.

In its most recent renaissance we replaced the supersonic jet with a surface mount and explored the dynamics of surface-induced dissociation occurring on a monolayer of a C12 perfluoroalkylthiol self-assembled on gold [72]. Particularly interesting dynamical features detected in these experiments included "skittering" of ions nearly parallel to the surface at the full translational energy of the incoming primary ion and primary ions scattered (desorbed) from the surface with thermal energy. The latter corresponds to the accommodation of ions on the surface with the loss of all their original kinetic energy. These are minor features; the main dynamical result is that SID is highly inelastic and a large fraction of the initial kinetic energy is lost to the surface along with significant angular scattering, both of which change with ion impact energy. Highly inelastic parent ions and fragment ions recoil from the surface with the same velocity, establishing that SID is best described as following a two-step mechanism (for the small molecular ions studied to date). Specifically, internal excitation in the surface collision is followed by unimolecular decay of the excited ion after it leaves the surface. It appears that SID collisional activation shares many characteristic features with gas phase CID.

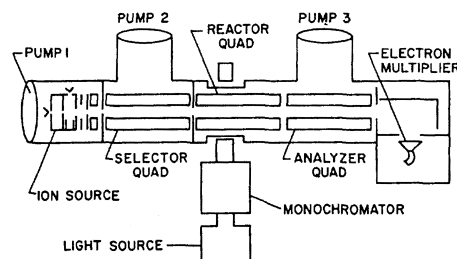At about the same time we were completing the

Fig. 5. 1975 triple quadrupole mass spectrometer.

Fig. 4 crossed-beam tandem construction project Professor Jim Morrison of Monash University was a sabbatical leave visitor at the University of Utah. While teaching us the wonders of quadrupole mass filters (and introducing us to what became an alternative version of SIMION) we were inspired to construct the first triple quadrupole tandem mass spectrometer. Jim Morrison, Austin Wahrhaftig, Cal Blakley, and Marvin Vestal were the intellectual drivers to construct a relatively low energy tandem mass spectrometer based on this concept. Another sabbatical leave visitor, Gerard Mauclair from Orsay, joined us in this project. Fig. 5 shows this pioneering example of a triple quadrupole apparatus schematically [73]. As in subsequent examples the first quadrupole is operated as a mass selector, the second is the rf only reaction region and the third stage is the mass analyzer. The quads were fabricated in the departmental shop using Jim Morrison's design.

Our scientific objective for the Fig. 5 apparatus was to investigate photodissociation of mass selected ions in the center storage quadrupole. We were ultimately successful in this endeavor, despite the experimental inconvenience of having to suppress ion–molecule reactions, especially collisional dissociation, occurring in the middle quadrupole. These were interesting phenomena that were not explored further in our laboratory for largely pragmatic reasons. Marvin carried this apparatus (and Cal Blakeley) with him to the University of Houston when he entered the academic phase of his own distinguished career. Jim constructed an improved version at Monash University fitted with a relatively powerful laser for ion photodissocation studies. He also described the Utah

apparatus in a seminar at Michigan State. Professor Chris Enke paid close attention and sent his talented graduate student Rick Yost to Monash to do the first CID experiments using a triple quadrupole in the Morrison laboratory. Shortly thereafter Enke and Yost constructed an optimized version at Michigan State and created a new subfield of mass spectrometry.

5. Collisional activation tandem mass spectrometry

Although our interest was ion–molecule chemistry, the central focus of tandem mass spectrometry became and remains collisional activation of ions to obtain structural information or unambiguous identification of target molecules. Although our first paper on tandem mass spectrometry used the electric sector of a double-focusing instrument to characterize metastable ions (and we introduced a collision cell into the field-free region of such an instrument in 1967), we did not pursue high-energy collisions until much later. Keith Jennings, Fred McLafferty, John Beynon, and Graham Cooks provided early and long-term leadership in collisional activation, sometimes emphasizing instruments and sometimes applications. The application of tandem quadropoles pioneered by Enke, Yost, Cooks, and others and the introduction of tandem in time experiments using ion traps and Fourier transform mass spectrometry further enriched the field.

Our recent role in collisional activation tandem mass spectrometry has been fundamental studies of energy transfer and ion dissociation. We have studied these phenomena using the same general approaches we had applied to ion–molecule reaction dynamics. In the mid-1980s we were intrigued by apparent differences in spectra obtained in triple quadrupoles versus high energy multiple sector instruments. [A round-robin experiment conducted by NIST to define the reproducibility of obtaining secondary ion spectra from collisional activation, which simply instructed investigators to optimize their experiments led to a variation of 3000 in relative peak heights for a test compound. Evidently either CID experiments were strongly instrument (or investigator) dependent or the
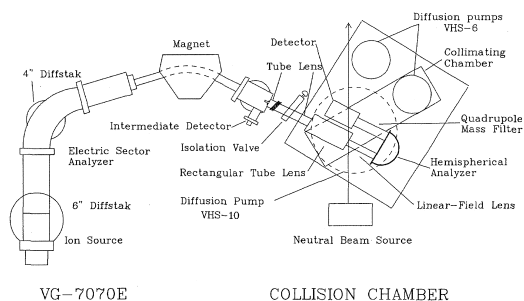

Fig. 6. 1988 tandem hybrid crossed-beam mass spectrometer.

essential mechanism changed dramatically with collision energy.] The desire to resolve this mystery (and others) motivated the construction of an instrument to investigate collisional activation over the kinetic energy range of a few electron volts to kilovolts.

A tandem instrument specifically designed for investigating the dynamics of collision- induced dissociation of polyatomic ions over decades of kinetic energy was under construction in 1986 when my research group moved to the University of Delaware. My principal collaborator in creating this instrument, shown schematically in Fig. 6 [74], was Research Professor Anil Shukla. Anil was particularly well qualified for this task, having already carried out a series of insightful CID experiments in the laboratories of Tony Stace and Keith Jennings.

The Fig. 6 tandem hybrid instrument has characteristics similar to the Fig. 4 crossed-beam apparatus but has much greater mass range and mass resolution. In particular the ion gun is a commercial double focusing mass spectrometer, explicitly a VG 7070E spectrometer. By using rectangular slot lenses similar to those shown for the Fig. 1 instrument we could reduce ion energy from 3000 to less than 1 eV at the collision center [75]. By this time an early version of SIMION program affirmed and improved our ion optics designs. The unique geometry of the Fig. 6 device with ion and neutral beams traveling in differing planes required complex mathematical transformations for data analysis and their presentation as Newton diagrams. However, by 1987 the combination of talented students and computers made this relatively straightforward. Anil and I worked together

quite closely to force agreement between optical design and experiment. At one point he reminded me of John Beynon's philosophy that one can design but not perform a perfect experiment and we should get some data. We followed his sage advice.

Our first research interrogated the CID of acetone and propane molecular cations [76]. Although energetically similar, their CID characteristics were totally different. A clue, which Anil brought to us, was that the CID and kinetic energy spectra of acetone were difficult to rationalize within the framework of the statistical quasi-equilibrium theory–Rice-Ramsperger-Kassel-Marcus (QET-RRKM) theory of mass spectra. In contrast, propane cation is the benchmark QET-RRKM molecular ion.

Further work with the Fig. 6 tandem instrument solved the puzzle by demonstrating unequivocally that acetone ions dissociate mainly by excited state pathways. The long-lived A state of the acetone cation exhibits CID dynamics that completely distinguish them from ground state acetone ions. By lowering the ion kinetic energy in several small steps below 0.5 eV and varying electron energy in the ion source, we demonstrated that exchange between electronic and translation energy is extremely efficient [76–79]. This totally unexpected facile interconversion of electronic and translational energies has since been confirmed for many other systems [80–86]. Certainly the discovery that electronically excited state pathways may be followed in low energy CID is one of the principal legacies from a dozen years of operation of this instrument.

An especially interesting dynamics feature of CID of triatomic ions revealed that using these instruments is full validation of a stripping/knock-out model [87]. For CID of CS_2^+ to form $S^+ + CS$ with argon scattering gas, we reached the remarkable conclusion that the system jumps from the ground state to the electronically excited C-state prior to the collision in which momentum is conserved. This sets the "timing" of the transition at the uncertainty principle limit, leading to the conclusion that energy transfer in a collision can occur in less than 1 fs. To our knowledge this is the fastest known chemical activation collision on record.
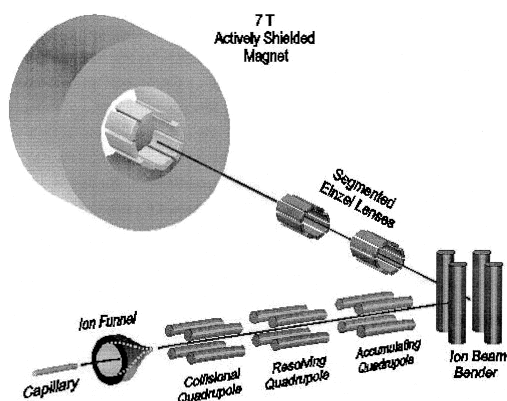

Fig. 7. Schematic of the millennium tandem mass spectrometer.

Bringing the tandem story to a close in this centennial year we have three new tandem instruments under construction at the W.R. Wiley Environmental Molecular Sciences Laboratory. They are clearly traceable to projects that were in progress at the University of Delaware but exploit effectively the expertise of our new colleagues in the Pacific Northwest. The concept of Fig. 7 describes an apparatus which we will commission in 2001. In the author's view this is the "ultimate" tandem mass spectrometer. As in previous tandem experiments, the ion source is modular and includes electron impact, chemical ionization, and electrospray ionization, with emphasis on the latter. Fig. 7 shows schematically the use of the electrospray ionization module. An rf/dc ion funnel transfers a very high fraction of electrosprayed ions into a low-pressure region in which the ion trajectories are relaxed by a rf-only quadrupole. This is followed by a lower pressure mass selector quadrupole, and a second rf-only collision quadrupole, which once again relaxes ion trajectories and serves as an ion storage device for pulsed ICR measurements. This is followed by a 900 beam deflector energy selector, two beam shaping elements (which can also function as ion traps) and a special eight electrode ICR cell within a 7T actively shielded superconducting magnet.

6. Epilogue

Since this incomplete story of the development and deployment of tandem mass spectrometers for the

investigation of fundamental collision properties of ions has spanned almost 40 years it is of interest to recount the recycling of several of the instruments described in this narrative. The Fig. 1 tandem was left in the capable hands of Dr. Tom Tiernan and transferred with him to Wright State University when he was appointed Director of the Brehm Laboratory and Professor of Chemistry in 1971. Although gathering dust it is, in principle, in good working order. The tandem ICR was recycled to Professor John Wronka at Northeastern University and recycled by him to my former Postdoctoral Fellow Vince Anicich at the Jet Propulsion Laboratory, where it is still used occasionally. The supersonic jet crossed-beam apparatus moved with us from Utah to Delaware and has been recycled to former Postdoctoral Fellow and Assistant Professor Helen deClercq at Howard University. The triple quadrupole was used briefly at the University of Houston, and was left behind when Marvin resigned his academic post and formed a company to commercialize thermospray sampling of ions from liquids. Presumably it has been recycled as components. The Delaware CID apparatus has been similarly decommissioned and is being scavenged for useful parts.

Acknowledgements

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