

TRIPLE-STAGE PENTAQUADRUPOLE (QqQqQ) MASS SPECTROMETRY AND ION/MOLECULE REACTIONS

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The general concepts, advantages, and applications of pentaquadrupole mass spectrometry and of a variety of pentaquadrupole multidimensional triple-stage (MS^3) scans as applied to the study of gas-phase ion/molecule reactions are reviewed. An overview is presented of the development and the present stage of triple-stage pentaquadrupole mass spectrometry, and examples of successful applications of “QqQqQ-MS” in revealing, elucidating, and helping to consolidate new classes of gas-phase ion/molecule reactions are summarized. The variety of features and advantages that make pentaquadrupoles most suitable laboratories for studies of ion/molecule reactions, and the exceptional gains in chemical information and selectivity of QqQqQ-MS are also discussed. © 1997 John Wiley & Sons, Inc., Mass Spectrom Rev 16, 113–144, 1997

I. INTRODUCTION

Ion/molecule reactions [Franklin, 1992; Bowers, 1979; Harrison, 1983; Futrell, 1986; Graul & Squires, 1988] in the gas phase are a subject of ample importance in chemistry, and interest in the fundamental aspects and applications of these collision processes has increased steadily since the pioneering work of Thomson [1913], Dempster [1931], Talrose [1952], Munson and Field [1966], and others. The important role of such reactions is demonstrated by their outstanding capabilities in characterizing via structurally diagnostic chemical reactivity a gaseous ionic species specified by its m/z ratio or, alternatively, a neutral molecule via its characteristic reactivity towards ions of known structure. In spite of the great success of mass spectrometry (MS) in elucidating the structure* of chemical compounds via dissociative ionization, conventional single-stage MS alone cannot provide information on the structures of the molecular and fragment ions formed, which are only characterized according to their m/z ratios. Collision-induced dissociation (CID) [McLafferty, 1983; Leusen & Schwartz, 1983; Holmes, 1985] of mass-selected ions, and other related dissociative collision double-stage MS^2 techniques [Busch, Glish, & McLuckey, 1988], provide a basis in MS for structural characterization of ions and, consequently, of the neutral molecules from which they are derived, thus greatly expanding the applicabilities of this remarkably useful technique. Ion/molecule reactions are useful alternatives to the use of dissociative collisions for MS determination of the structures of gaseous ions. Ion/molecule reactions performed in MS environments also provide one of the best-known connections between gas-phase and condensed-phase chemistry, and are exceptionally valuable for studying the intrinsic properties of isolated, long-lived, “solvent-free” ions. In the case of an ionic reaction occurring in the condensed phase, the solvent and counterion usually have

significant effects on reaction properties. On the other hand, ion/molecule reactions of gaseous ions yield a wealth of kinetic, thermochemical, and structural information in a more direct fashion.

Ion chemistry studies in the gas phase are greatly refined by the use of double-stage (MS^2) mass spectrometers [Busch, Glish, & McLuckey, 1988] that are able to produce and to “purify” through mass selection the desired ions of chosen m/z ratios, and to perform dissociative or reactive collisions with specific neutral molecules under controlled conditions. Different physical principles, each presenting specific benefits and drawbacks, are applied to promote reaction and to separate and characterize reactant and product ions according to their *mass-to-charge* (m/z) ratios before and after the collision process. The triplequadrupole mass spectrometer (QqQ) [Yost & Enke, 1983] displays several characteristics that have made it outstanding as a MS^2 instrument. Triplequadrupoles have shown remarkable ability to efficiently perform the whole set of MS^2 experiments in a *tandem-in-space* mode, insensitivity for mass analysis to ion kinetic energy that gives unit mass resolution before and after collisions, high ion transmission of the “rf-only” quadrupole reaction cell, high tolerance to poor vacuum, and ease of operation and software control. Additionally, collision energies can be varied from zero to a few hundred eV with ease, thus permitting access to reactive and dissociative collisions. The “energy-resolved” MS (ERMS) [McLuckey et al., 1982] technique has taken advantage of the easy control of collision energies in triplequadrupoles to provide more detailed information on ion dissociation behavior. Triplequadrupole experiments are also invaluable for ion/molecule reaction studies, and can provide information on precursor and product ions via operation in several different MS^2 scan modes. Additionally, its *tandem-in-space* mode of operation very much simplifies spectral acquisition. The limitations inherent to triplequadrupoles when used in ion/molecule reaction studies includes the fact that the two stages of mass analysis (MS^2) do not allow any access to structural information on reaction products of mass-selected ions.

Such a limitation of triplequadrupoles (QqQ) is removed by the use of a more complex but considerably more powerful multiquadrupole arrangement, the *Pentaquadrupole Mass Spectrometer* (QqQqQ) or simply “*Pentaquadrupoles*” (see Fig. 1) [Morrison, Stanney, & Tedder, 1986; Beaugrand et al., 1986; Schwartz, Schey, & Cooks, 1990; Juliano et al., 1996]. Pentaquadrupoles employ an ion source, two “full ion transmission” reaction quadrupoles, known as ion-focusing or “rf-only” quadrupoles (q2 and q4), and three independently operable mass-analyzing quadrupoles (Q1, Q3, and Q5). Their “on-line” *tandem-in-space* arrangement allows the study of reactions of mass-selected ions that occur in sequence in the two separate reaction regions by using all three stages of mass

* The term “structure” is used in a restrictive sense to denote the connectivity of atoms rather than detailed structure.

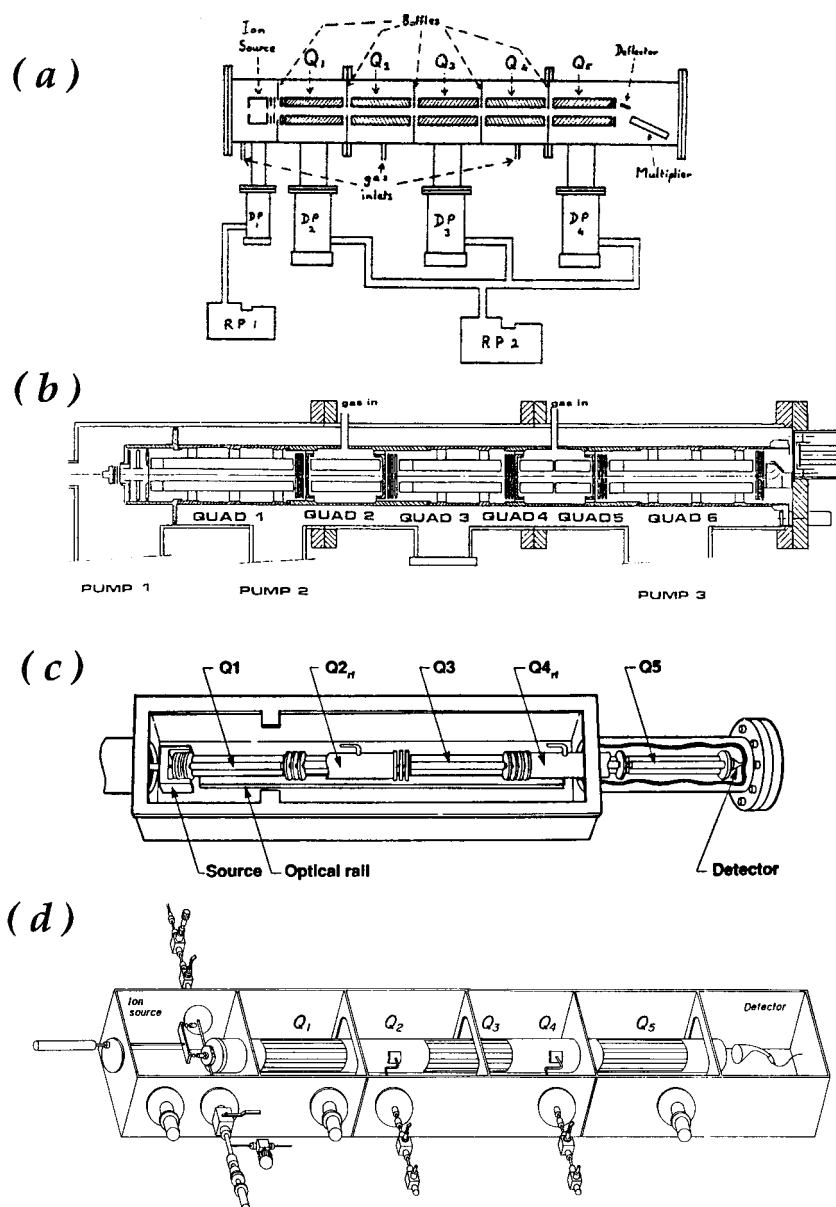


FIGURE 1. Schematics of pentaquadrupole mass spectrometers as reported by (a) Morrison, (b) Rolando, (c) Cooks, and (d) Eberlin, and co-workers. Note in Figs. (a), (c), and (d) the “on-line” arrangement of the three mass-analyzers (Q_1 , Q_3 , and Q_5) and two “rf-only” quadrupole reaction chambers (Q_2 and Q_4), and the double q_4/q_5 reaction cell in Fig. (b). In a typical ion/molecule reaction experiment in pentaquadrupoles, ions are generated in the ion-source, “purified” (mass-selected) by Q_1 , and reacted with a neutral gas introduced in Q_2 under controlled conditions (collision energy, pressure, and sometimes reaction time). Product ions are subsequently mass-selected by Q_3 , and structurally analyzed by either collisional dissociation or structurally diagnostic ion/molecule reactions in Q_4 , whereas the products formed in these processes are disclosed by scanning Q_5 . Adapted from References 3, 51, 78 and 83.

analysis. Given, therefore, the ability to either mass-analyze or to mass-select ions before and after each of the reaction regions, a powerful and diverse set of MS^3 experiments is available [Schwartz et al., 1990]. These experiments allow access to very specific types of information about gas-phase ion/molecule reactions, including their

ionic intermediates, connecting processes, the structures of the reaction products, and significant advantages in terms of chemical selectivity. The pentaquadrupole is also particularly useful for multiple-stage MS^3 , because it allows the full range (all 15 types) of MS^3 experiments [Schwartz et al., 1990] (as well as all the experiments of

lower mass dimensionalities) to be easily accessed. It also allows either ion/molecule reactions or CID to be performed in either of the two separate reaction regions. Also, by scanning sequentially, synchronously, or simultaneously two or all three of the mass-analyzing quadrupoles, a variety of three-dimensional (3D) and, remarkably, a 4D mass spectrum [Juliano et al., 1996] can be obtained; each spectrum provides specific and detailed information about the processes under investigation. In spite of the fact that three stages of ion mass analysis and two stages of CID or ion/molecule reactions are performed in pentaquadrupole MS^3 experiments, MS^3 scans can still be performed quickly and with high overall ion transmission, provided that high-transmission quadrupoles and adequate computer control and MS^3 software are employed [Juliano et al., 1996].

Thus, in pentaquadrupoles, ions can be efficiently generated in the ion source, purified via mass-selection in Q1, reacted in q2 under controlled conditions, including collision energy, concentration of reactant neutral gas pressure, and even reaction time in the special trapping version of the experiment [Beaugrand et al., 1989; Juliano, 1996; Ranasinghe, Cooks, & Sethi, 1992], and further mass analysis of the reaction products in Q3. Each individual ionic product can be mass-selected by Q3 and characterized according to specific chemical reactivity or CID behavior in q4/Q5. The whole set of data can be collected and presented in the form of multidimensional spectra for easy visualization. Additionally, secondary ions can be produced via either CID or ion/molecule reactions, or primary ions can be collisionally activated or deactivated by collisions in q2, and their dissociation or chemical reactivity studied further in q4. Pentaquadrupoles are, therefore, very useful devices and are certainly one of the most complete laboratories for the studies of gas-phase ion/molecule reactions. Note that all these steps are performed “on-line” in very short time intervals, and under conditions that can be maintained for long periods and that are easily described and reproduced.

This review will provide an overview of the development and the present stage of pentaquadrupole MS with particular reference to its advantages and specific applications in the study of gas-phase ion/molecule reactions.

II. PENTAQUADRUPOLE: AN HISTORICAL VIEW

Instrumental and conceptual developments that led to *pentaquadrupoles* have been naturally linked to the more general development of multiple stage MS [Busch, Glish, & McLuckey, 1988]. Fundamental applications of metastable ion MS (or “MIKES”) [Hipple & Condon, 1945; Cooks et al., 1973], particularly to ion structure characterization

and its analytical application to mixture analysis [Kruger et al., 1976], provided the base from which MS/MS was to evolve. This process led to the introduction of a series of MS/MS instruments that includes the triplequadrupole [Yost & Enke, 1983], which was used for the first time for MS/MS by Yost & Enke [1978]. The QqQ in turn, together with continuing interest in sector instruments [Busch, Glish & McLuckey, 1988] for MS/MS, led to the development of MS^n scans, many of which were discussed in conjunction with the development of the hybrid BEQQ instrument [Schoen et al., 1985]. These developments created the appropriate climate in which the pentaquadrupole was introduced. In this context, just as single quadrupole mass spectrometers (Q) were developed so successfully into triplequadrupoles (QqQ), so a similar expansion of QqQ to pentaquadrupoles (QqQqQ) was naturally expected.

The first pentaquadrupoles [Figs. 1(a) and (b)] were assembled and concurrently described together with a few of the first experimental results by two groups, *viz.* Morrison, Stanney, & Tedder [1986] and Beaugrand, Devant, Nermag, & Rolando [Beaugrand et al., 1986] during the 1986 ASMS conference. The authors realized the potential of the many possible MS^3 operating modes of pentaquadrupoles and that they offer a “unique and comprehensive study of both primary and secondary ion structure, derived from collisionally activated fragmentation and/or selective ion molecule reactions” [Morrison, Staddey, & Tedder, 1986]. According to Morrison, Staddey, & Tedder [1986], the main advantages of pentaquadrupoles were centered basically on the facts that “it adds little in complexity, but enhances the scope of the instrument considerably. This . . . also makes possible more complex ion reaction studies and MS/MS/MS. . . . The equipment costs much less (than FTICR’s), data acquisition is much simpler, while the instrument can tolerate vacua of up to 10^{-4} torr.” It was also stated by Beaugrand et al. [1986] that “More possibilities are offered by the various scanning modes available with such a machine and they will have to be investigated.” As this review shows, the advantages and outstanding capabilities anticipated for pentaquadrupoles have been amply demonstrated since that time.

Although a few pentaquadrupole MS^3 scans were demonstrated by Beaugrand et al. [1986], it was only in 1989 with the “overnight” assembly by Schwartz and Schey [Schwartz, Schey, & Cooks, 1990] of the “Cooks’ pentaquadrupole” [Fig. 1(c)] that the full range of new multiple stage, multidimensional pentaquadrupole MS^3 scans were implemented, and their applications, particularly to the study of ion/molecule reactions, amply demonstrated. Cooks and Enke [Schwartz et al., 1990] also outlined a systematic basis of multiple stage MS, developing a complete methodology for representing, categorizing, and understanding multiple stage MS and their

multidimensional scan modes. This basis has been very useful in guiding the studies and applications of pentaquadrupole MS.

However, overall ion transmission in MS³ pentaquadrupole experiments was naturally low, and performing some multidimensional MS³ scans was time-consuming because of data averaging and spectrum accumulation routines that were often required. Ion transmission is diminished in pentaquadrupoles by the three stages of ion mass analysis and by the ion current depletion that occurs in the two reaction regions. For the 3D scans, for which two mass analyzers are synchronously or sequentially scanned over a full mass range of interest, quite long acquisition times, normally more than an hour, were often required for the acquisition of the whole domain of data. Recently, however, a high-transmission pentaquadrupole mass spectrometer [Juliano et al., 1996] was reported [Fig. 1(d)], in which very fast multidimensional (3D and 4D) mass spectra with much improved *signal-to-noise* ratios are acquired. Very satisfactory transmissions in the MS³ modes have been obtained by the use of the high-transmission $\frac{3}{4}n$ Extrel quadrupoles, whereas adequate computer control and software development allowed very fast acquisition of the complete domain of data for several 3D, and remarkably for the first 4D mass spectra. The one key design feature of the system was the use of $\frac{3}{4}n$ diameter poles. The MS/MS transmission for $\frac{1}{4}n$ poles is about 10% at *m/z* 219 (FC-43), but greater than 50% for the larger $\frac{3}{4}n$ poles. This factor equates to an approximately 1% transmission for a $\frac{1}{4}n$ pentaquadrupole and a 25% transmission for a $\frac{3}{4}n$ pentaquadrupole.

Acquisition times of triple-stage mass scans in the pentaquadrupole were substantially reduced by the implementation of a selective prescan procedure, used for instance in the case of a familial scan (see Fig. 2) to identify, prior to spectral acquisition, ions for selection by Q1. Thus, Q5 was scanned only when Q1 was set exactly at the masses of the preselected precursors. As a consequence of these developments, the complete set of MS³ scans are now readily available in pentaquadrupoles, which enhances considerably the applicability of QqQqQ MS. In the following section, examples of the applicability of such scans to ion/molecule chemistry studies will be presented. These applications clearly demonstrate the extraordinary gain in chemical information and selectivity of pentaquadrupole MS.

III. TRIPLE STAGE (MS³) PENTAQUADRUPOLE SCANS AND APPLICATIONS

Detailed and very specific information about ion/molecule reaction processes can be conveniently collected via a vari-

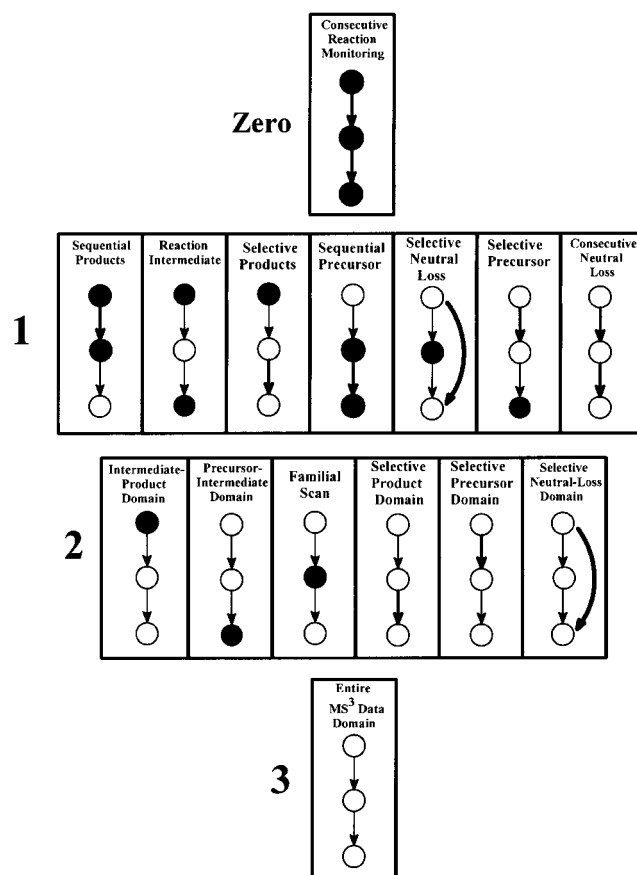


FIGURE 2. Symbols and names given to the complete set of MS³ experiments having zero, 1, 2, and 3-mass dimensions. A circle represents a mass analyzer in operation that transmits either a fixed mass (filled circle) or variable masses (open circle), whereas the arrows indicate the ion course; thick arrows denote fixed mass transitions, and variable mass transitions are expressed by thin arrows. Adapted from Reference 84.

ety of triple-stage pentaquadrupole scans of 0, 1, or 2 mass dimensions that produce either 2-, 3-, or 4-D mass spectra (one ion abundance axis and the remainder mass axes). Following the methodology for representing, categorizing, and understanding MSⁿ scans proposed by Cooks and Enke [Schwartz et al., 1990], there exist 15 different MS³ scans for which symbols and names are given in Fig. 2. Note that, given the ability to perform either ion/molecule reactions or CID in either of the two separated quadrupole reaction cells (q2 and q4), there still exists in pentaquadrupoles the possibility to perform four versions of each of the original set of MS³ scans. The efficient performance of a number of MS³ scans has been accomplished in pentaquadrupoles, and their utility in the study of ion/molecule reactions has been systematically evaluated. Pentaquadrupole MS³ scans also have been successfully applied for the study of consecutive CID processes [Schwartz, Schey, & Cooks, 1990; Juliano, 1996; Majumdar et al., 1991;

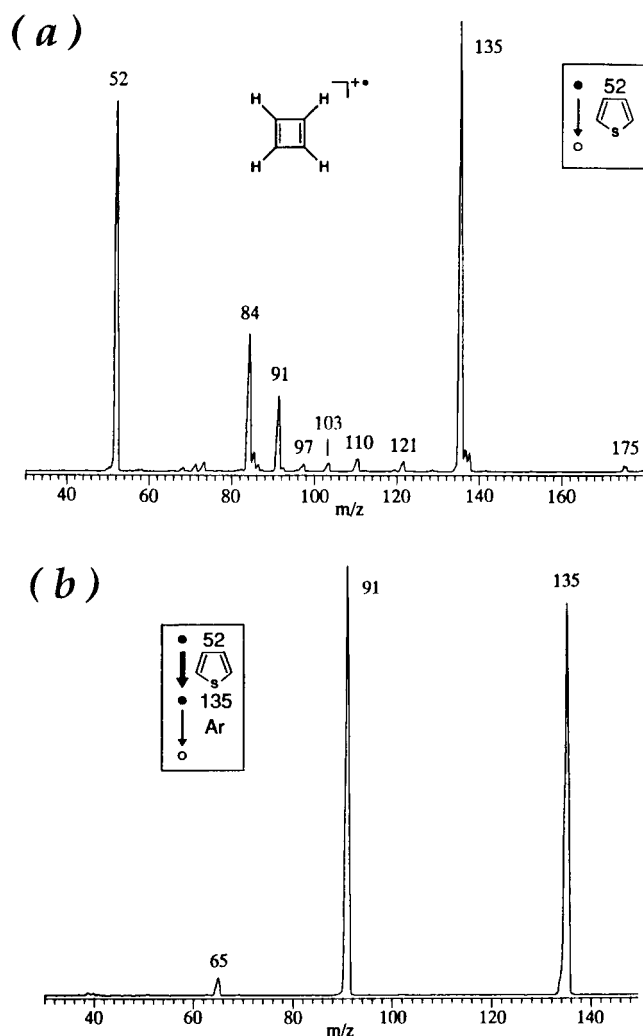


FIGURE 3. (a) Pentaquadrupole double-stage (MS^2) product spectra for ion/molecule reactions of ionized cyclobutadiene (m/z 52) with thiophene; and (b) triple-stage sequential product spectrum of the product of m/z 135. Adapted from Reference 85.

Grant & Cooks, 1990; Gozzo & Eberlin, 1995], but this review will be restricted to applications in ion/molecule reaction studies.

A. MS^3 Terminology

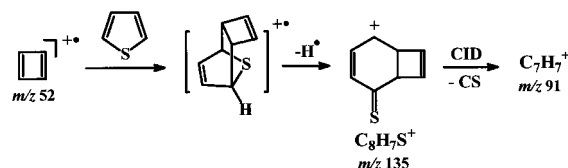
In the terminology used to describe MS^n scans [Schwartz et al., 1990], a circle represents a mass analyzer in operation that is set either to transmit ions of a selected mass (filled circle), or to scan over a full mass range of interest, thus transmitting variable masses (open circle). The neutral collision gas that causes the mass transitions (which most often occur either via mass loss in CID or mass gain in ion/molecule reactions) is shown between the circles.

Arrows are used to indicate the ion course; thick arrows denote that the mass transition is fixed by the two fixed masses it connects, whereas a variable mass transition is represented by thin arrows, although in several cases this differentiation is dispensable. Because all data produced by MS^3 scans of lower mass dimensions are contained in one or more of the MS^3 scans of higher mass dimensionality, it is also possible via a number of useful *projection* and *extraction* operations to obtain data of lower dimensionality from higher dimensional scans. All this latter information is available without the need of any further experiments.

B. Sequential Product Scan

The first MS^3 experiment to be described [Jennings, 1966; Burinsky et al., 1982; Cody et al., 1982] has also been shown to be one of the most useful for ion/molecule reaction studies. This usefulness is because in sequential product scans each product of the reaction of a mass-selected ion can be characterized according to either its specific chemical reactivity or its CID behavior. Cooks [Shay et al., 1992] reported the first triple-stage pentaquadrupole spectra produced by such a scan. As seen in Fig. 3(a), ionized cyclobutadiene of m/z 52 reacts readily with thiophene, likely by [2 + 1] cycloaddition, followed by rapid hydrogen atom loss and dissociation of the nascent cycloadduct to afford the main product ion of m/z 135. The application of the sequential product scan [Fig. 3(b)] shows that the product ion dissociates exclusively to m/z 91 by CS neutral loss. From these and several other items of information collected from MS^3 scans, the reaction scheme summarized in Scheme 1 was proposed. Similar results were obtained in reactions with furan.

An interesting variation of the sequential product scan [Eq. (1)] was also introduced in this study, in which the effects of changing the *internal energy* of the reactant ion prior to ion/molecule reaction were investigated. In this experiment, $C_4H_4^+$ ions [Shay et al., 1989] were mass-selected by Q1 and Q3, whereas collisions with cyclohexane were carried out in q2 at variable low energies. The surviving $C_4H_4^+$ ions arriving from Q3 were subjected to ion/molecule reactions in Q4 with allene. Therefore, an



SCHEME 1.

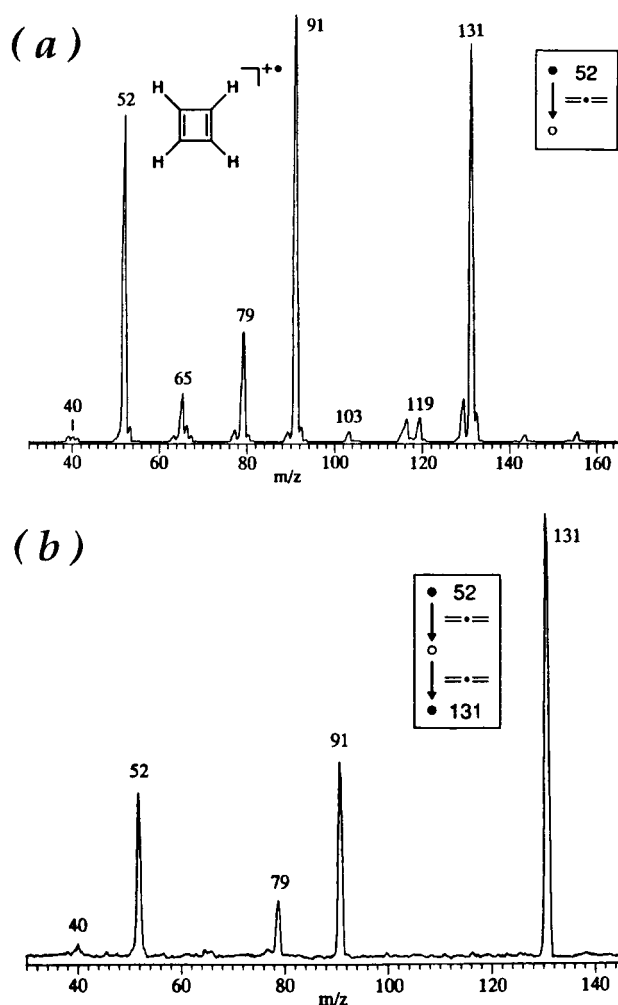
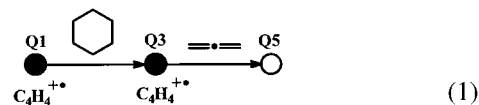


FIGURE 4. (a) Pentaquadrupole double-stage (MS^2) product spectrum for ion/molecule reactions of ionized cyclobutadiene (m/z 52) with allene; and (b) triple-stage (MS^3) reaction intermediate spectrum for the intermediates connecting the m/z 52 precursor and the m/z 131 product. Adapted from Reference 85.

opportunity was provided in $q2$ for collisional activation or deactivation of the reactant ions. The results indicated an absence of any significant internal energy effects on the ion/molecule reactivity of these $C_4H_4^{++}$ ions. This interesting application of the sequential product scan has been employed in a number of other studies with similar results [Sorrilha et al., 1996; Eberlin, Majumdar, & Cooks, 1992; Gozzo & Eberlin, 1995; O’Lear et al., 1987]. It is interesting to note here that, although ion/molecule reactivity is expected to be influenced to a considerable extent by the internal energy of the reactant ions [Bowers, 1979], this factor seems not to affect considerably the chemistry observed in quadrupole collision cells. The substantial delay between ion activation and subsequent reactive collisions as well as the “near zero” energy and relatively high-pressure multiple collision conditions normally used to

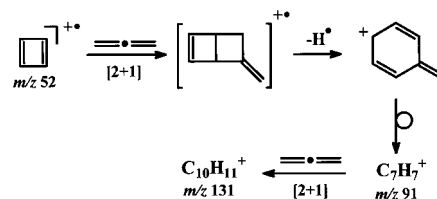
carry out reactions in quadrupole cells may alleviate internal energy effects by promoting collisional “cooling” of the reactant ion.



C. Reaction Intermediate Scan

This MS^3 scan can be efficiently performed in pentaquadrupoles [Schwartz, Schey, & Cooks, 1990] by scanning $Q3$ while $Q1$ and $Q5$ are set to select particular ions, and CID or ion/molecule reactions are executed in $q2$ and $q4$. It is helpful when defining the characteristics of the reaction intermediate scan [O’Lear et al., 1987] to emphasize that the intermediates detected by $Q3$ must simultaneously be products of the selected precursor specified by $Q1$ and precursors of the product ion finally specified by $Q5$. Note here the inherent difficulties in performing such a scan in “tandem-in-time” mass spectrometers. This interesting scan mode is particularly useful when ionic intermediates in ion/molecule reactions are to be investigated.

Figure 4(a) [Shay et al., 1992] shows the pentaquadrupole product spectrum for ion/molecule reactions of ionized cyclobutadiene of m/z 52 with neutral allene (40u). Note that the multiple collision conditions used lead to various products, of which m/z 131 is the most abundant. An example of the first set [Shay et al., 1992] of reaction intermediate spectra employed to reveal intermediates in ion/molecule processes is shown in Fig. 4(b). Ion/molecule reactions with allene were performed in $q2$ and $q4$ while the cyclobutadiene ion of m/z 52 and the ion/molecule product of m/z 131 were mass-selected in $Q1$ and $Q5$, respectively. Such an experiment allows one to obtain from the MS^3 spectrum the masses (actually the m/z ratios) of all intermediates that connect the selected precursor and final product ion, or, in other words, all the intermediates that arise from the precursor ion of m/z 52 and that subsequently react to yield the product ion of m/z 131. The major intermediate is m/z 91, which indicates a two-step $[2 + 1]$ cycloaddition process for the formation of the m/z 131 product (Scheme 2). The minor intermediates of



SCHEME 2.

m/z 40 and 79 seen in the spectrum also reveal the operation of a secondary reaction pathway to m/z 131 formation [Shay et al., 1992].

D. Three-Dimensional Familial Scan

When a specific intermediate ion is selected by Q3 and Q1 and Q5 are both scanned across mass ranges of interest, then the three-dimensional (3D) MS³ scan known as the “familial” scan is performed. The term *familial* has been chosen [Schwartz et al., 1990] because by this scan one can interrogate the relationship of all “products” and sequential products to the particular intermediate product ion selected in Q3. As for the majority of other MS³ scans, several different combinations of ion/molecule reactions and CID can be applied in q2 and q4. Performing ion/molecule reactions in q2 and CID in q4 would reveal via their dissociation chemistry the structure of ionic products of the mass specified by Q3 that are formed from each specific precursor specified by Q1. No example of this specific version of the familial scan has been so far reported. The opposite combination, on the other hand, tells a related but quite different story. It was performed in a pentaquadrupole to acquire the first familial scan [Eberlin, Majumdar, & Cooks, 1992] applied to ion/molecule reaction studies (Fig. 5). In this experiment, 3-octanone ions were formed in the ion source via 70 eV dissociative ionization, and ions of m/z 43 were selected as the fixed intermediates in Q3. In the spectrum, the angled “Q1” axis displays the precursors that form by CID the intermediate ions of m/z 43, whereas the horizontal “Q5” axis displays the ion/molecule products arising upon reaction with isoprene of the m/z 43 ions generated from each specific precursor detected by Q1. Note that four CID precursors of m/z 43 are identified along the Q1 axis; that is, m/z 71, 72, 85, and 99. It is also evident from the 3D plot that m/z 43 ions formed from different precursors react quite differently with isoprene, and hence they probably possess different structures. It has been determined that the acetyl cation ($\text{CH}_3\text{—C}^+=\text{O}$) reacts with isoprene to form an abundant $[4 + 2^+]$ cycloadduct of m/z 111 (see the ion/molecule reaction section that follows), whereas other $\text{C}_2\text{H}_3\text{O}^+$ isomers and the C_3H_7^+ isobar react predominantly by proton transfer that leads to a series of products of which m/z 81 is the most abundant. Ions of m/z 43 formed by CID from the m/z 85 and 72 precursors react with isoprene to form predominantly the ionic product of m/z 111, which proves that this subset of m/z 43 population is composed mainly of the acetyl cation. On the other hand, the product of m/z 81 is dominant in the spectrum displayed along the Q5 axis for the ions of m/z 43 generated from the m/z 99 and 71 precursors, whereas no product of m/z 111 is formed. Thus, the m/z 43 populations in

both these cases do not include the acetyl cation, and mechanistic considerations indicate that C_3H_7^+ is the main ion of m/z 43 that is formed from these specific precursors.

E. Sequential Precursor Scan

The value of extracting data of lower mass dimensionality from higher dimensional scans is demonstrated by the sequential precursor spectra shown in Fig. 5(b) and Fig. 5(c) [Eberlin, Majumdar, & Cooks, 1992]. This MS³ scan has proven very useful for ion chemistry studies, because it can record subsets of isobaric or isomeric ionic populations that are selected on the basis of a specific chemical reactivity or dissociation behavior. They can be recorded directly, or alternatively, several of them can be extracted from either the 3D precursor-intermediate spectrum or the familial spectrum (Fig. 2). Extractions from the 3D familial spectrum along the Q5 axis at the fixed masses of m/z 81 and 111 produce the sequential product spectra shown in Figs. 5(b) and 5(c), respectively. Figure 5(b) records the subset of the m/z 43 population identified by their precursors (m/z 72 and 85) that reacts with isoprene to form the $[4 + 2^+]$ cycloadduct of m/z 111; that process, therefore, characterizes the acetyl cation. Conversely, formation of the main product of the proton transfer sequence of m/z 81 [Fig. 5(c)] identifies the subset of the m/z 43 population not composed of the acetyl cation, and shows it to be comprised of those ions generated by CID from m/z 71 and 99 precursor ions. Even the small contribution of m/z 72 to Fig. 5(c) is consistent with the acetyl cation, because minor proton transfer also occurs for this ion. Note also that *extractions* along the Q5 horizontal axis can produce a variant of the *sequential product spectrum*, in which the chemical reactivity of an ion generated by CID from a specific precursor is displayed.

F. Four-Dimensional Entire MS³ Data Domain Scan

Sequential scanning of all three mass analyzers leads to the acquisition of a 4D mass spectrum that contains the entire MS³ domain of data for the processes under investigation. Figure 6(a) presents schematically the first example [Juliano et al., 1996] of such a 4D spectrum, and several lower-dimensional spectra that can be *extracted* or *reconstructed by projection* from it. Each of the cyclopentanone 70 eV EI ions formed in the ion-source was selected individually in Q1, and submitted in q2 to near-zero eV ion/molecule reactions with 2-methyl-1,3-dioxolane. The product ions formed in such reactions were mass-selected, again individually (one at a time) in Q3, and subjected to 10 eV CID with argon in q4, while Q5 recorded each individual CID spectrum. All data concerning the cyclo-

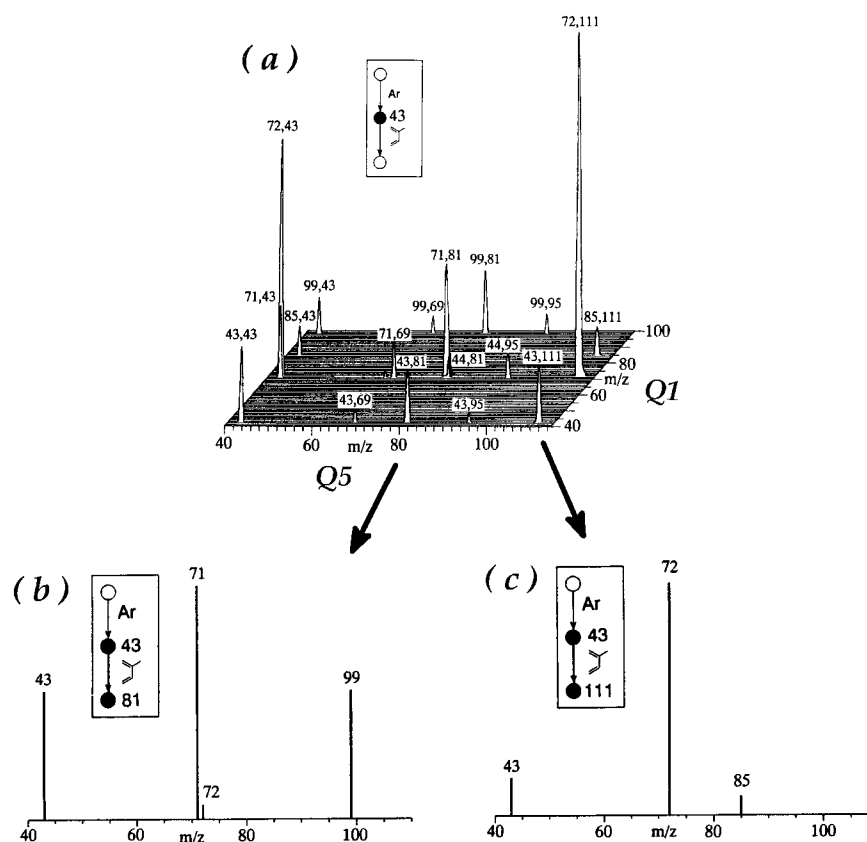


FIGURE 5. (a) Pentaquadrupole three-dimensional triple-stage (MS^3) familial spectrum for 3-octanone ions acquired by selecting ions of m/z 43 as the intermediates. The angled Q1 axis displays the precursors of m/z 43 ions, whereas the horizontal Q5 axis displays the ion/molecule products of these CID-generated m/z 43 ions arising from reactions with isoprene. Triple-stage sequential precursor spectra extracted from the 3D familial spectrum by selection in Q5 of the final products of (b) m/z 81 and (c) m/z 111. Adapted from Reference 22.

pentanone ion/molecule products and their relative abundances, each of them directly associated with their dissociation products, are, therefore, contained in the 4D spectra.

G. Three-Dimensional Intermediate-Product Domain Scan

Unfortunately, it is not possible to conveniently display all four dimensions of the 4D spectrum; hence, more specific information and a partial, but better, visualization of the 4D data must be obtained by extracting data of lower dimensionality, as exemplified in Fig. 6(b) for the 3D intermediate-product domain spectrum. This spectrum [Juliano et al., 1996] was obtained by extracting data that fall in the hatched plane that is defined by the simple equation $m/z_{Q1} = 55$. Therefore, data that are related specifically to the Q1-mass selected m/z 55 ion are displayed. In other words, these data correspond to a scan mode in which the m/z 55 ion is mass-selected in Q1, and Q3 and Q5 are

both sequentially scanned. A detailed and complete view of the whole ion/molecule process for the m/z 55 ion is, therefore, seen in this spectrum. Across the diagonal line in Fig. 6(b), in which equal masses in Q3 and Q5 are selected, the remaining reactant ion (m/z 55) that survives collisions in q2 and all its reaction products with 2-methyl-1,3-dioxolane are displayed (m/z 73, 87, 89, and 99). On the other hand, the CID spectrum of each individually selected product can be seen across the Q5 axis. The α - β unsaturated acylium ion $CH_2=CH-C^+=O$ of m/z 55 reacts readily with the cyclic acetal 2-methyl-1,3-dioxolane by transacetalization to afford the product ion of m/z 99. (For details of this new gas-phase reaction, see the following section). As seen in Fig. 6(b), the m/z 99 product ion fragments extensively by C_2H_4O neutral loss (44u); that process most likely regenerates the reactant ion of m/z 55. Another interesting feature of this 3D spectrum is that it also allows one to interrogate the identity of the reactant ion from which all the other product ions are

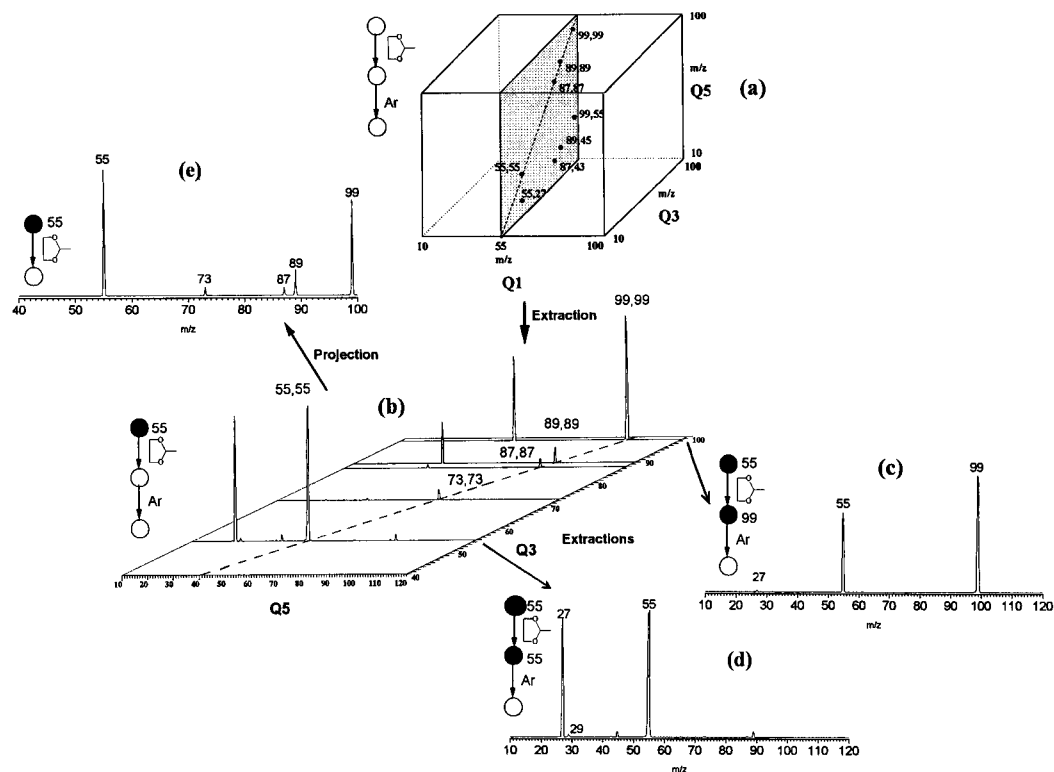


FIGURE 6. (a) The first 4D triple-stage (MS^3) spectrum (abundance axis is not included) obtained in a pentaquadrupole by sequential scanning of all three mass analyzer quadrupoles, which contains the entire MS^3 data domain for cyclopentanone ions. (b) 3D triple-stage (MS^3) intermediate product domain spectrum, which was extracted from the 4D spectrum along the hatched $m/z_{Q1} = 55$ plane. Extracted 2D triple-stage (MS^3) sequential product spectra of (c) the m/z 99 reaction product, and (d) the m/z 55 reactant ion. (e) Reconstructed (by projection towards the Q3 axis) 2D double-stage (MS^2) product spectrum of the m/z 55 ion. Reproduced with permission from Reference 51.

derived. The m/z 55 ion is shown to fragment extensively to m/z 27 by neutral CO loss, which is the dissociation process expected from its α - β -unsaturated acylium ion structure $CH_2=CH-C^+=O$.

Extraction from the 3D spectrum along the Q5 axis (fixed Q3 masses) produces **2D sequential product spectra**, which are exemplified for the product ion of m/z 99 in Fig. 6(c) and for the reactant ion of m/z 55 in Fig. 6(d). These spectra are useful for structural assignments, because the dissociation chemistry of each ion/molecule product and additionally that of the reactant ion are displayed separately in the 2D plots. Note that the spectrum shown in Fig. 6(d) is equivalent but not identical to a conventional **product spectrum**, because the precursor ion of m/z 55 undergoes nondissociative low energy collisions in q2 prior to CID in q4 ($55 \rightarrow 55 \rightarrow$ products).

An additional and interesting feature of the 3D intermediate-product domain spectrum is the possibility to reconstruct the **product spectrum** of the m/z 55 ion [Fig. 6(e)] by *projection* towards the Q5 axis [Juliano et al., 1996]. *Projection* is simply accomplished by adding to the

abundance of the surviving ions the abundance of their corresponding fragments. Therefore, in the reconstructed spectrum, the effect of depletion of the relative abundance of the product ions caused by fragmentation in q4 is canceled out, and the corrected yields of the ion/molecule products are displayed.

H. Consecutive Neutral Gain/Neutral Loss (NGNL) Scan

Figure 7 shows another MS^3 spectrum that can be extracted from the 4D spectrum. Data *extraction* was performed along the line defined as the intersection between the two hatched planes described by the equations: $m/z_{Q3} = m/z_{Q1} + 44$ and $m/z_{Q5} = m/z_{Q3} - 44$. The resulting spectrum [Fig. 7(b)] [Juliano et al., 1996] is a version of the **consecutive neutral loss scan** (Fig. 2), where a specific neutral gain/neutral loss sequence is monitored. Only the cyclopentanone ions that react with 2-methyl-1,3-dioxolane in q2 to yield products corresponding to a 44u mass gain, and that further dissociate upon collision with argon in q4 by neu-

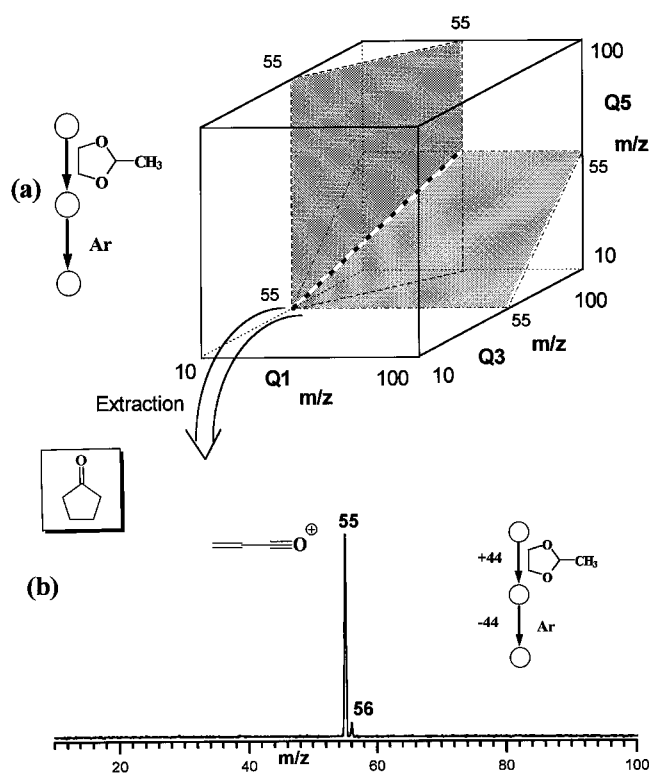


FIGURE 7. (b) Pentaquadrupole triple-stage (MS^3) consecutive 44u neutral gain/neutral loss (NGNL) spectrum, which was extracted from the (a) 4D spectrum along the intersection between the two planes described by the equations $m/z_{Q3} = m/z_{Q1} + 44$ and $m/z_{Q5} = m/z_{Q3} - 44$. Reproduced with permission from Reference 51.

tral loss also of 44u are displayed in this spectrum. As seen in Fig. 7(b), this scan mode is very selective and structurally diagnostic for acylium ion, because only the $\text{CH}_2=\text{CH}-\text{CO}^+$ ion of m/z 55 (and a mixture of mainly its ^{13}C and ^2H isotopes of m/z 56) respond to the test. It undergoes a consecutive neutral gain/neutral loss of 44u due to transacetalization (net 44u addition) and dissociation of the product by $\text{C}_2\text{H}_4\text{O}$ (44u) neutral loss. Consecutive NGNL MS^3 scans have also been performed directly for a series of compounds (Fig. 8), clearly selecting by this very specific reaction/dissociation sequence the acylium ions formed.

IV. ION/MOLECULE REACTIONS IN PENTAQUADRUPOLES

Gas-phase ion/molecule reactions [Franklin, 1972; Bowers, 1979; Harrison, 1983; Futrell, 1986; Graul & Squires, 1988] have been observed and studied by mass spectrometry since its very infancy, as exemplified by the classical reaction of H_2 self-protonation that led to the disturbing observation of the H_3^+ product ion in the pioneering mass

spectrum of molecular hydrogen collected by Thomson [Thompson, 1913]. Mechanisms of ion formation [Smyth, 1931] of H_3^+ , I_3^+ , and H_3O^+ and the earliest theory describing ion/molecule reactions [Eyring, Hirschfelder, & Taylor, 1936] were published before 1940. In the 1950s, improvements in vacuum technology and electronics supplied researchers with a much more controlled environment in which they could perform such reactions, and the field flourished from then on. Most of the studies on ion/molecule reactions have been performed in ion cyclotron resonance mass spectrometers [Farrar & Saunders, 1988] and in high-pressure chemical ionization sources [Harrison, 1983]. Although triplequadrupole mass spectrometers were introduced as early as 1972 [Yu et al., 1972; Vestal & Futrell, 1974; McGilvery & Morrison, 1978] it was late in that decade before it was used for MS/MS [Yost & Enke, 1978], and only in the 1980s that researchers realized the convenience of using the central “ion focusing” quadrupole as a low-energy reaction chamber

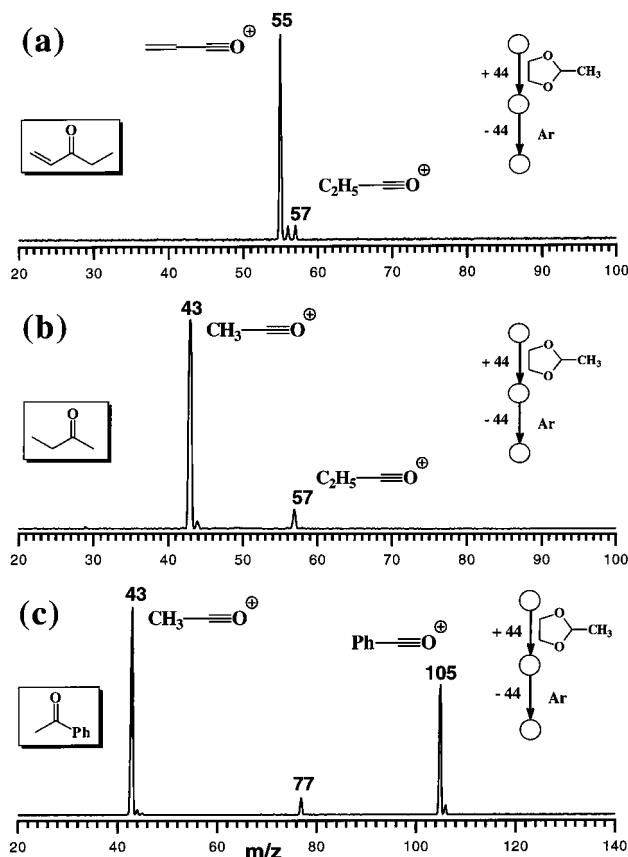


FIGURE 8. Pentaquadrupole triple-stage (MS^3) consecutive 44u neutral gain/neutral loss (NGNL) spectra applied for the ions produced from EI of (a) ethyl vinyl ketone, (b) 2-butanone, and (c) acetophenone. Note that the three mass-analyzer quadrupoles were simultaneously scanned to acquire such a spectrum, and that only acylium ions respond readily to the 44u NGNL test. Reproduced with permission from Reference 51.

to study ion/molecule reactions [Morrison, Stenney, & Tedder, 1981; Jalonen, 1985; Kinter & Bursey, 1986; Graul & Squires, 1990; Heath, Allison, & Watson, 1991; Kenttämää & Cooks, 1989; Fetterolf, Yost, & Eyler, 1984]. The advantages for ion chemistry studies of an “on-line” arrangement of two reaction chambers intercalated by three mass analyzers was soon realized, and pentaquadrupoles appeared [Morrison, Stanney, & Tedder, 1986; Beaugrand et al., 1986; Schwartz, Schey, & Cooks, 1990; Juliano et al., 1996]. Presently, a number of investigators are exploring the vast capabilities of pentaquadrupole MS for the study of ion/molecule reactions.

The example of Fig. 9 [Sorrilha et al., 1996] shows a series of MSⁿ (*n* = 1–3) scans that provides a classical illustration of the study of ion/molecule reactions in pentaquadrupoles. Ions are produced in the ion-source from a specific precursor (a). A desired ion is mass-selected by Q1 (b), and is reacted with a specific neutral reactant in q2 (c). Reaction conditions such as collision energy and the pressure of the reactant neutral as well as tuning conditions are adjusted to maximize reaction yields. Reaction products of interest can be mass-selected by Q3 (d), and dissociated or (e) reacted further with a second neutral reactant in q4, while Q5 is scanned to record the triple stage spectrum. Note that differential pumping minimizes cross-contamination problems. Additionally, an ion/molecule reaction already investigated in the reaction quadrupole can, in some cases, be adequately performed in the ion source under CI conditions. The ionic products can be mass selected and reacted with a second neutral in q2; the product of interest is mass-selected by Q3 (f) and further collisionally dissociated in q4 (g). Again, more specific information can be obtained by applying other scan modes to access, for instance, reaction intermediates, “familial” relationships, or to display data three-dimensionally. As the following examples will show, pentaquadrupole MS has been applied not only to expand the knowledge and applicability of already-established reactions, but especially to reveal, to elucidate, and to help consolidate new classes of gas-phase ion/molecule reactions.

A. [2 + 1] Cycloaddition of Ionized Cyclobutadiene

The MS³ capabilities of the pentaquadrupole mass spectrometer were applied, for the first time to a significant problem of ion/molecule chemistry, by Shay et al. [1992]. In this introductory study, the ion/molecule chemistry of four C₄H₄⁺ isomers (see below) with allene, isoprene, furan, and thiophene was systematically investigated. The potential of the pentaquadrupole in differentiating the ions and in providing mechanistic insights for a complex system of isomers that may readily equilibrate was established.

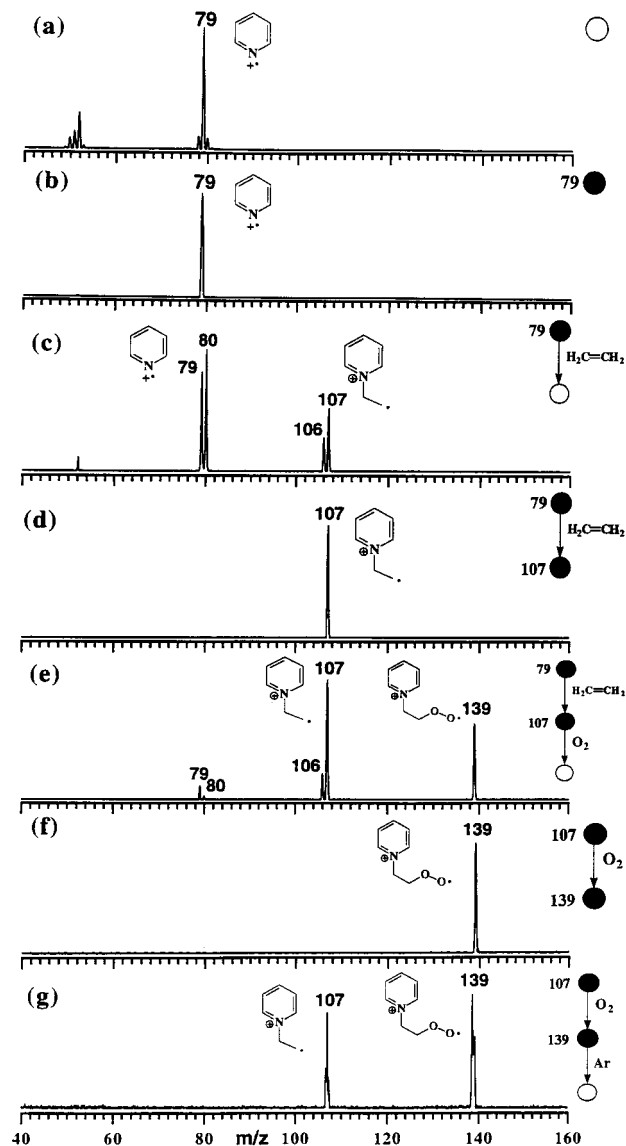
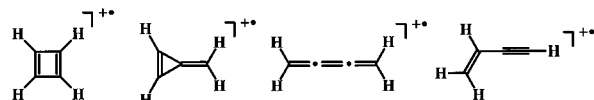


FIGURE 9. Sequence of pentaquadrupole MSⁿ (*n* = 1 – 3) scans applied to studies of gas-phase ion/molecule reactions. Ionized pyridine (*m/z* 79) is (a) produced by 70 eV EI of the neutral, (b) mass-selected by Q1, and (c) reacted with ethylene in q2. The reaction product of *m/z* 107 (**10**) is (d) mass-selected by Q3, and (e) reacted further with O₂ in q4, while the triple-stage sequential product spectrum is acquired by Q5. To acquire the dissociation spectra of the oxygen adduct, the initial reaction with ethylene was performed in the ion source under CI conditions, the product ion of *m/z* 107 was reacted in q2 with oxygen, and (f) the adduct of *m/z* 139 was mass-selected in Q3, and dissociated further by (g) CID with argon in q4. Reproduced with permission from Reference 88.



The C₄H₄⁺ ions were shown to undergo structurally

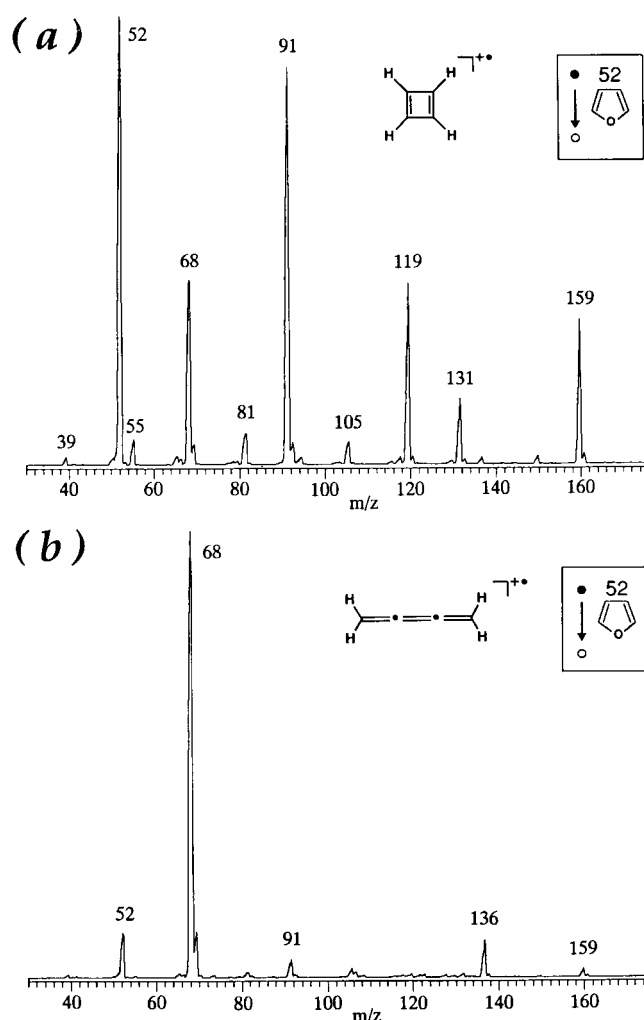


FIGURE 10. Pentaquadrupole double stage (MS^2) product spectra for ion/molecule reactions of (a) ionized cyclobutadiene (m/z 52) and (b) ionized butatriene with furane. Reproduced with permission from Reference 85.

diagnostic ion/molecule reactions; the most characteristic reactivity was displayed by the nonaromatic ionized cyclobutadiene ion. That ion undergoes a series of probable $[2 + 1]$ cycloaddition reactions with allene [see Fig. 4(a) and Scheme 2], isoprene, furan [Fig. 10(a)], and thiophene [see Fig. 3(a) and Scheme 1]. The nascent cycloadducts dissociate rapidly, isomerize, or undergo further addition reactions; thus, a complex set of products was often obtained. As exemplified in Fig. 10(a), reactions of ionized cyclobutadiene with neutral furan yield a variety of abundant products, amongst which one finds the $[2 + 1]$ cycloaddition/dissociation product of m/z 119. The other $C_4H_4^+$ isomers [Fig. 10(b)] react mainly by charge exchange (m/z 68). From several MS^3 experiments, some of which have already been discussed, mechanistic and structural information on the products were provided, and

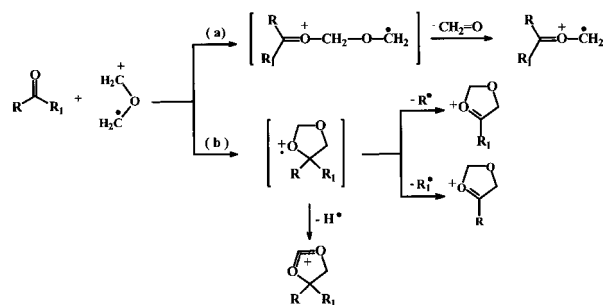
the results were summarized in reaction schemes such as that shown in Scheme 1. Bakhtiar, Drader, & Jacobson [1993] applied these structurally diagnostic reactions to prove that ionized cyclobutadiene is formed in reactions of atomic transition metal cations with *cis*-3,4-dichlorocyclobutane.

B. $[3 + 2]$ 1,3-Cycloadditions of the Simplest Ionized Carbonyl Ylide $CH_2=O^+-CH_2$

Pentaquadrupole MS has also been applied to study the gas-phase reactions of the *ylidium* or α -distonic [Hammerum, 1988] ion $CH_2=O^+-CH_2$ (or $^+CH_2-O-CH_2$); i.e., the ionized form of the simplest carbonyl ylide [Eberlin et al., 1997]. The results provide experimental (and *ab initio* theoretical) evidence for a novel $[3 + 2]$ 1,3-cycloaddition in the gas phase; that is, the first example of cycloaddition involving an ionized carbonyl ylide. Cycloaddition (b) of $^+CH_2-O-CH_2$ that occurs across the $C=O$ bond of several carbonyl compounds was shown to compete with electrophilic addition (a) to the carbonyl oxygen (Scheme 3), and to be favored for reactants bearing electron-withdrawing substituents. The nascent cyclic and acyclic adducts, formed in exothermic reactions with excess internal energy, both undergo complete dissociation to cyclic 4-substituted-1,3-dioxolanylium ions and ionized methylene (CH_2^+) transfer products, respectively.

As an example of this type of reactivity, the product spectra for reaction of $^+CH_2-O-CH_2$ with acetone, trifluoroacetone, and cyclopentanone are shown in Fig. 11. Note the competition between CH_2^+ transfer (m/z 72) and cycloaddition (m/z 87) for acetone, whereas the cycloaddition/dissociation products of m/z 155 and especially m/z 87 dominate for the “cycloaddition-activated” trifluoroacetone. $[3 + 2]$ Cycloaddition also dominates for cyclopentanone, and two products formed upon “reaction-induced” dissociation of the nascent bicyclic spiroadduct (Scheme 4) are observed in the product spectrum [Fig. 11(c)].

Pentaquadrupole triple-stage sequential product scans



SCHEME 3.

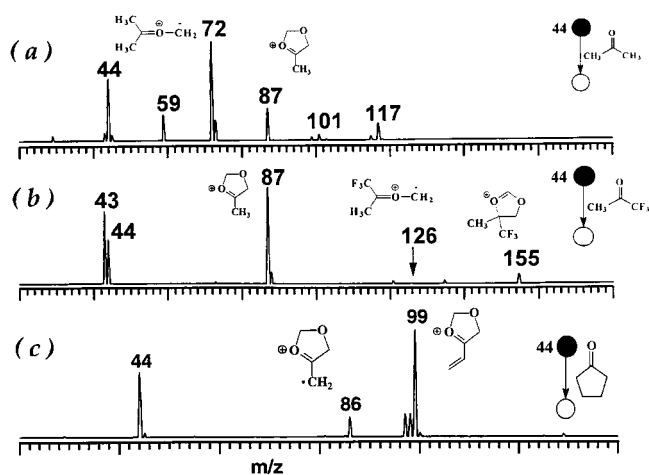


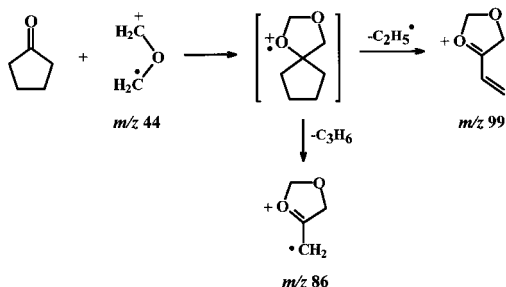
FIGURE 11. Pentaquadrupole double-stage (MS^2) spectrum for ion/molecule reactions of $^+CH_2-O-CH_2$ with (a) acetone, (b) 1,1,1-trifluoroacetone, and (c) cyclopentanone. Adapted from Reference 24.

were applied for the characterization of the cycloaddition products. Dissociations that correlate well with the proposed cyclic structures and with that of isomeric and reference ions were observed. Figure 12(a) shows the triple-stage spectrum of the cycloaddition/dissociation product of acetophenone, and the double-stage dissociation spectra of an isomeric [Fig. 12(b)] and an authentic (an ion whose structure is known with confidence) ion [Fig. 12(c)]. Note the distinct dissociation seen in Figs. 12(a) and 12(b) and the almost perfect match of Figs. 12(a) and 12(c).

C. Polar $[4 + 2^+]$ and $[4^+ + 2]$ Cycloadditions

1. Acylium and Thioacylium Ions

Ion/molecule reactions performed via pentaquadrupole MS have been successfully applied to differentiate, on the basis of distinct $[4 + 2^+]$ cycloaddition reactivity, the CH_3-CO^+ member of the classical set of $C_2H_3O^+$ iso-



SCHEME 4.

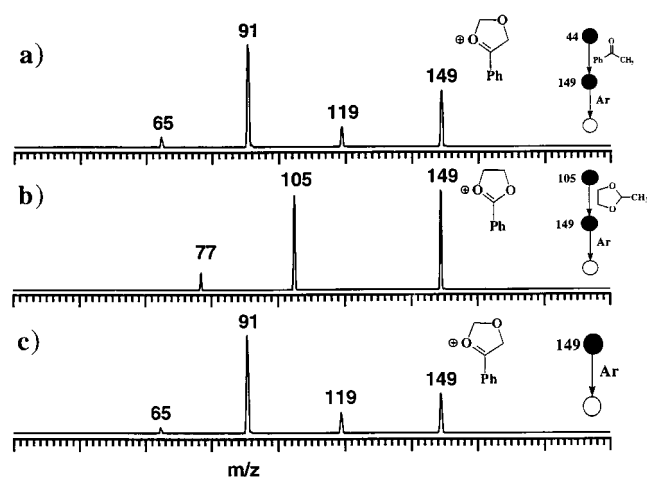


FIGURE 12. Pentaquadrupole triple-stage (MS^3) sequential product spectrum (a) of the product of m/z 149 formed in $[3 + 2]$ cycloaddition of $^+CH_2-O-CH_2$ to acetophenone and (b) of the isomeric ion of m/z 149 formed via transacetalization of 2-methyl-1,3-dioxolane with $Ph-CO^+$ (m/z 105), and (c) double-stage dissociation spectrum of a reference ion. Reproduced with permission from Reference 24.

mers, of which the most stable structures are shown below [Eberlin, Majumdar, & Cooks, 1992].

In reactions with isoprene, the acetyl cation $CH_3-C^+=O$ [Fig. 13(a)] was shown to be unique in that it reacts to a great extent by a novel polar $[4 + 2^+]$ cycloaddition (Scheme 5), whereas the two other $C_2H_3O^+$ isomers as well as the $C_3H_7^+$ isobar react mainly by proton transfer. The extent to which ions of m/z 43 undergo cycloaddition (m/z 111) or proton transfer reaction (from which the secondary product of m/z 81 is the most abundant) with isoprene was shown to provide quite precise estimates of the acetyl ion composition. Thus, a m/z 111/81 ratio of 10 was proposed to characterize the “pure” acetyl cation. Sequential product scans [Fig. 13(b)] show, as one would expect [Turecek & Hanus, 1984], that the cycloadduct dissociates upon collision exclusively by the retrocycloaddition process (Scheme 5). Comparison, via pentaquadrupole MS^3 experiments, of the dissociation of the cycloadducts under very similar collision conditions to those displayed by loosely bound species such as proton-bound dimers, provides evidence for the covalently bound nature of the products.

Familial scans (see Fig. 5), as already discussed, have also been applied to determine the composition, via this structurally diagnostic ion/molecule reaction, of m/z 43 ions generated by “on-line” CID from specific precursors. Egsgaard and Carlsen [1995] applied this structurally diagnostic reaction to demonstrate that the $C_2H_3O^+$ chemion sampled from a premixed methane/oxygen flame is composed mainly by the acetyl cation.

Polar $[4 + 2^+]$ cycloaddition with a series of conju-

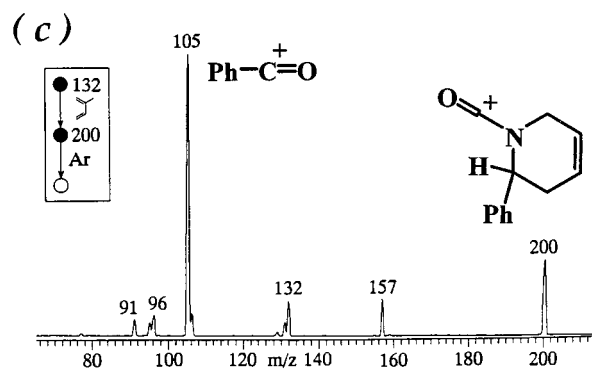
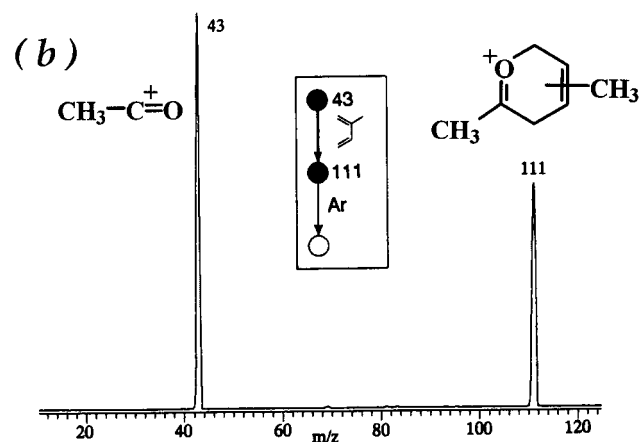
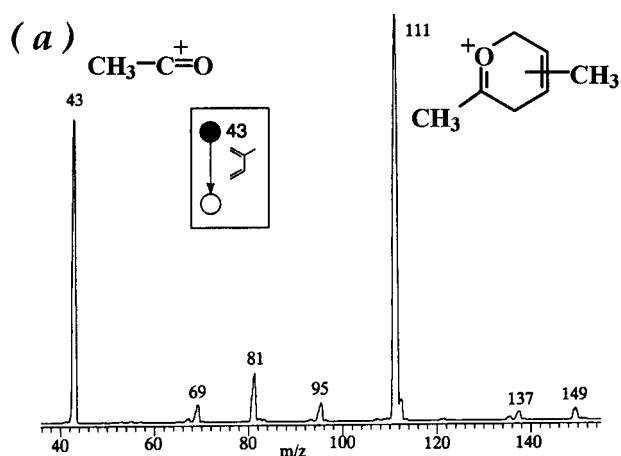
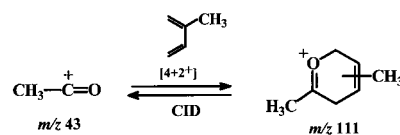


FIGURE 13. (a) Pentaquadrupole double-stage (MS^2) product spectra for ion/molecule reactions of $\text{CH}_3-\text{C}^+=\text{O}$ with isoprene; and triple-stage (MS^3) sequential product spectrum of the $[4+2^+]$ cycloadducts of $\text{CH}_3-\text{C}^+=\text{O}$ and $\text{Ph}-\text{CH}=\text{N}-\text{CO}^+$. Adapted from Reference 19.

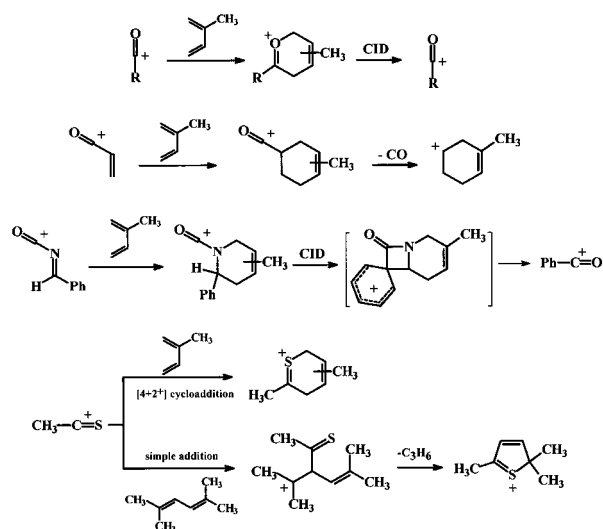
gated “s-cis” dienes was also verified by pentaquadrupole MS to be a general and dominant reaction for a variety of acylium ions [Eberlin & Cooks, 1993]. MS^3 experiments also show that cycloreversion dominates the dissociation chemistry of all the $\text{C}=\text{O}$ cycloadducts (Scheme 6). However, $[4+2^+]$ cycloaddition to the α,β -unsaturated acylium ions $\text{CH}_2=\text{CH}-\text{C}^+=\text{O}$ and $\text{Ph}-\text{CH}=\text{N}-\text{C}^+=$



SCHEME 5.

O occur not at $\text{C}=\text{O}^+$ but predominantly across the $\text{C}=\text{C}$ and $\text{C}=\text{N}$ double bonds, respectively. This change in reactivity was ascribed to activation of $\text{C}=\text{C}$ and $\text{C}=\text{N}$ double bonds towards cycloaddition that is promoted by the strongly electron-withdrawing positively charged CO^+ substituent. The nascent cycloadduct, in the particular case of $\text{CH}_2=\text{CH}-\text{C}^+=\text{O}$, undergoes extensive but not complete dissociation by CO loss (Scheme 6). Evidence that the m/z 95 ion is formed was provided by the MS^3 sequential product scan and comparison with a reference $\text{C}_8\text{H}_{13}^+$ ion. On the other hand, the MS^3 spectrum of the stable and abundant $\text{C}=\text{N}$ cycloadduct of $\text{Ph}-\text{CH}=\text{N}-\text{C}^+=\text{O}$ [Fig. 13(c)] shows it to dissociate upon collisional activation not by CO loss (a high-energy nitronium ion would be formed), but mainly to $\text{Ph}-\text{C}^+=\text{O}$ [Fig. 13(c)] likely via an interesting phenyl migration process that is comparable to some extent to processes in which phenyl groups provide anchimeric assistance (Scheme 6).

The activation (or deactivation effect) of a variety of positively charged substituents (Y^+) on polar $[4+2^+]$ cycloaddition occurring across $\text{C}=\text{C}$ double bonds of $\text{CH}_2=\text{CH}-\text{Y}^+$ ions has been recently investigated by pentaquadrupole MS [Moraes & Eberlin, to appear]. Also noteworthy is the reactivity of the thioacylium ion $\text{CH}_3-\text{C}^+=\text{S}$, which reacts by $[4+2^+]$ cycloaddition with the “s-cis” conjugated diene isoprene (Scheme 6)



SCHEME 6.

to a great extent, whereas reactions with the “s-trans” 2,5-dimethyl-2,4-hexadiene provide mainly the methylated 2,5-dimethyl thiophene cation [Paradisi et al., 1988]. Steric hindrance of the terminal methyl groups makes it difficult for the latter reactant to assume the “s-cis” conformation required for polar $[4 + 2^+]$ cycloaddition. Further pentaquadrupole MS studies have also demonstrated that polar $[4 + 2^+]$ cycloadditions occur extensively in the gas phase with a variety of nitrilium and immonium [Eberlin et al., 1995], sulfonium, protonated, and methylated carbonyl compounds [Lu et al., 1995], protonated azabutadienes [Augusti & Eberlin, 1994; Sparrapan et al., to appear], aza-benzynium ions [Gozzo et al., to appear], and with several of these ions with neutral “s-cis” heterodienes [Sorrilha et al., 1994].

2. Nitrilium and Immonium Ions

It was observed that polar $[4 + 2^+]$ cycloaddition of nitrilium and immonium ions [Eberlin et al., 1995] with isoprene occurs extensively when the HOMO(isoprene)-LUMO(ion) energy gap is small and the competitive proton transfer reaction is endothermic. Thus, the nitrilium ions $R-C\equiv N^+-CH_3$ ($R=H, CH_3CO, Br$) and $H-C\equiv N^+-C_2H_5$ as well as the immonium ions $CH_2=NH^+-R$ ($R=H, Ph, CH_3CO, CH=CH_2$) form abundant $[4 + 2^+]$ cycloadducts, whereas deactivated (large HOMO-LUMO gaps) nitrilium and immonium ions such as $C_2H_5-C\equiv N^+-CH_3$ and $(CH_3)_2-C=NH_2^+$ are practically unreactive towards cycloaddition and proton transfer. Several isomeric protonated nitriles $R-C\equiv N^+-H$ showed exothermic proton transfer as the main ion/molecule reaction. Isomeric distinction was shown to be straightforward in several cases, as demonstrated for instance for protonated acetonitrile and protonated isonitrile (Fig. 14). Note that such a drastic change in chemical reactivity upon different sites of “protonation” was also clearly observed in the case of O-protonated ketene $CH_2=C=O^+-H$ and C-protonated ketene; i.e., the acetyl cation $CH_3-C^+=O$ [Sorrilha et al., 1996]. As already mentioned, the former more acidic isomer reacts extensively with isoprene by proton transfer, whereas the latter reacts predominantly by polar $[4 + 2^+]$ cycloaddition. A rich dissociation chemistry, which correlates well with the proposed structures and proves their covalently bound nature, was often observed for the nitrilium ion cycloadducts, as exemplified in the sequential product spectrum shown in Fig. 15(a). Retrocyclization dominates, however, for the immonium ion cycloadducts [Fig. 15(b)]; that characteristic was also verified for an authentic cycloadduct formed upon protonation of 1,2,3,6-tetrahydropyridine.

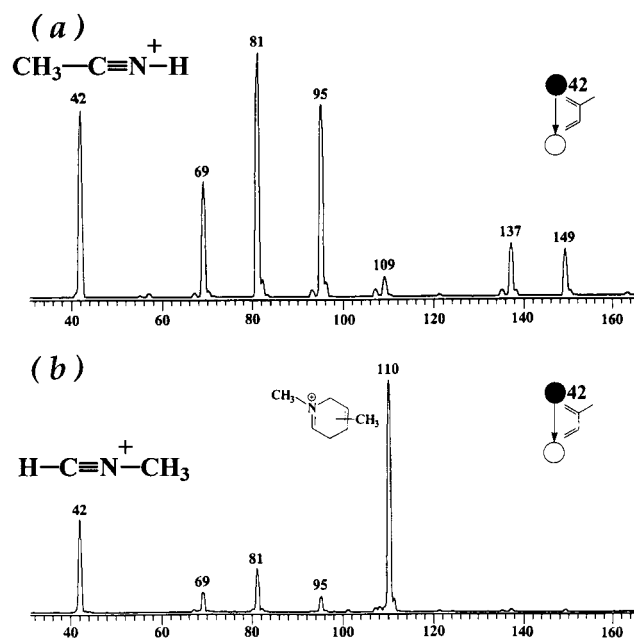


FIGURE 14. Pentaquadrupole double-stage (MS^2) product spectra for ion/molecule reactions of the two isomeric ions (a) $CH_3-C\equiv N^+-H$ and $H-C\equiv N^+-CH_3$ with isoprene. Adapted from Reference 23.

3. Protonated and Methylated Carbonyl Compounds

A variety of protonated and methylated carbonyl compounds were also found to undergo polar $[4 + 2^+]$ cycloadditions with three neutral “s-cis” conjugated dienes; that is, butadiene, isoprene, and 2,3-dimethoxybutadiene [Lu et al., 1995]. Two examples of such reactivity are presented in Scheme 7. The pentaquadrupole triple-stage spectrum of the protonated quinone/butadiene cycloadduct shows rich but quite limited dissociation that includes successive losses of CO and water molecules, thus proving its covalently bound nature while indicating that cycloaddition takes place across the $C=C$ double bond, as predicted by theoretical calculations. Dissociation chemistry that agrees in general with that of the putative $[4 + 2^+]$ cycloadduct was observed in the double-stage spectra of the authentic, “solution-synthesized” cycloadduct.

Cycloaddition reactivity for the protonated and methylated carbonyl compounds was also found to correlate well with HOMO-LUMO energy gaps. The lower cycloaddition reactivity of, for instance, the protonated and methylated 4-cyclopentene-1,3-dione when compared to protonated and methylated quinone, and the main dissociation of their cycloadducts by the retrocycloaddition process as observed in their triple-stage spectra, is consistent with their higher HOMO-LUMO energy gaps and the fact that stable aromatic adducts cannot be formed in these cases (Scheme 7).

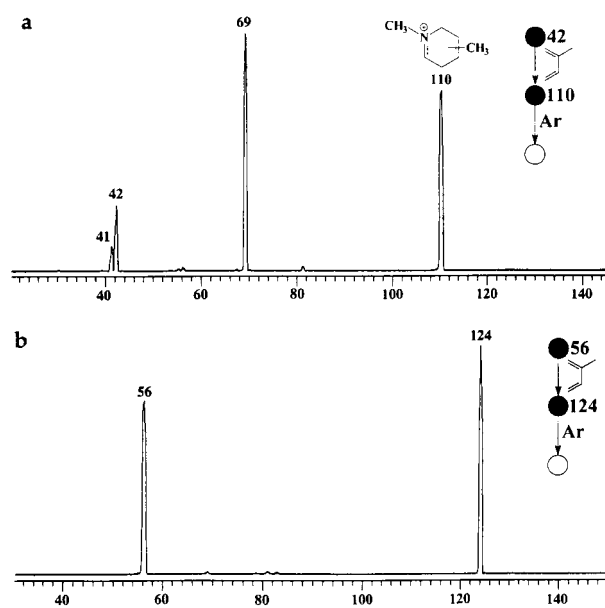
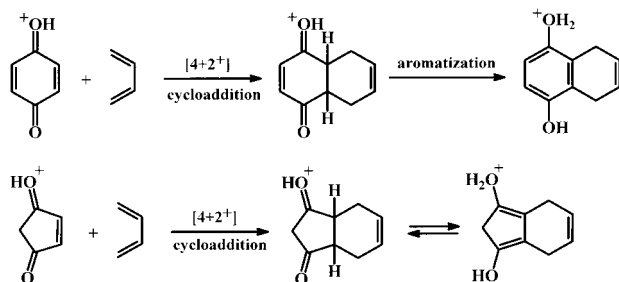


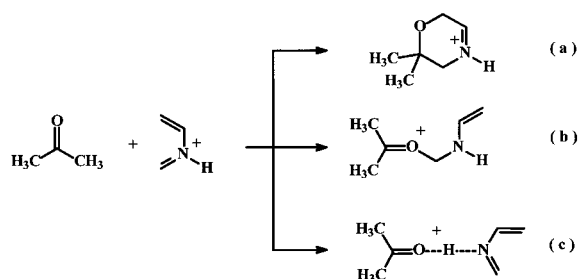
FIGURE 15. Pentaquadrupole triple-stage (MS^3) sequential product spectrum of the $[4 + 2^+]$ cycloadducts arising from ion/molecule reactions of (a) $CH_3-C\equiv N^+-H$ and (b) $CH_2=NH^+-CH=CH_2$ with isoprene. Adapted from Reference 23.

4. Protonated 1-Aza and 2-Azabutadiene

Azabutadienes are very useful dienes that participate in a number of synthetically important cycloaddition reactions in the condensed phase. Acidic media are often employed; hence, their protonated forms are the most likely reactant species. The simplest protonated 1-aza and 2-azabutadienes are formed easily in the gas phase from dissociative ionization of piperidine and allylamine, respectively. Their formation from these precursors is expected from simple dissociation mechanism considerations [Augusti & Eberlin, 1994], and has been supported by high-level G2 *ab initio* calculations [Sparrapan et al., to appear]. QqQq-MS was employed to investigate their tendency to undergo gas-phase cycloaddition with several dienophiles (substituted alkenes, ketones, ethers, nitriles, acetyl chloride, and sulfoxides). Adduct formation was observed in reactions



SCHEME 7.



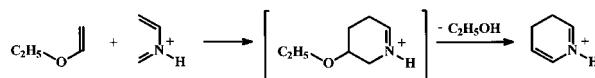
SCHEME 8.

with most of the dienophiles employed; those adducts were shown by MS^3 sequential product scans to dissociate exclusively by the “retro-addition” process. This simple dissociation chemistry does not allow differentiation between the three conceivable products (as exemplified for acetone and protonated 2-azabutadiene in Scheme 8); i.e., the cycloadduct (a), the simple addition product (b), and the proton-bound dimer or “the *mono-solvated ion*” (c).

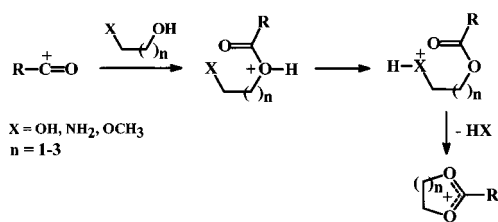
Ab initio calculations were performed to interrogate the most thermodynamically favorable products. Polar $[4^+ + 2]$ cycloaddition was shown as by far the most likely and most exothermic reaction in the cases of the substituted alkenes, and for the nitriles with protonated 2-azabutadiene. An experimental evidence for cycloaddition was provided by the reaction with ethyl vinyl ether (Scheme 9), in which no intact adduct but an abundant product corresponding to loss of an ethanol molecule from the adduct was formed. With a few exceptions, the other adducts were predicted by the *ab initio calculations* to be most likely the “*mono-solvated ions*” (c, Scheme 8). The dissociation exclusively to the original protonated azabutadiene reactant ions of these loosely bound proton-bound dimers, as seen in their MS^3 spectra, was found to be consistent with the much higher proton affinities of the neutral 1-aza and 2-azabutadienes when compared to that of all the neutral reactants [Sparrapan et al., to appear].

5. Aza-Benzynium Ions

Recently, Gozzo et al. [1997] reported the first experimental and theoretical evidence for the aryne nature of 2-pyridyl and 2-pyrimidyl cations, i.e., of L-aza- and 1,3-diaza-benzynium ions, respectively. Pentaquadrupole scans show the ions to react extensively with isoprene by polar $[4 + 2^+]$ cycloaddition to afford adducts that dissoci-

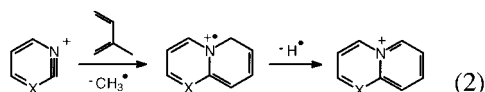


SCHEME 9.



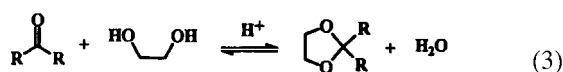
SCHEME 10.

ate rapidly by methyl and hydrogen atom loss; thus the aza-aromatic cations shown in Eq. 2 are formed.



D. Ketalization with Acylium Ions and Analogs

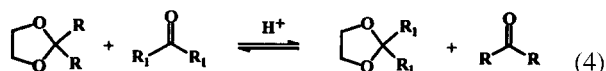
It has been recently demonstrated [Moraes, Pimpim, & Eberlin, 1996] via pentaquadrupole MS that acylium ions in the gas phase readily undergo a novel ketalization reaction with a variety of diols and their nitrogen and sulfur analogs and monoalkyl derivatives. In the condensed phase, ketalization (or acetalization) is a classic, very general, and synthetically useful reaction by which aldehydes and ketones are converted into cyclic acetals and ketals in reactions with diols [Eq. (3)]. These reactions are very effective in protecting either the carbonyl compounds or, alternatively, the diols against their most common reaction partners. The reactants are, however, easily reformed upon hydrolysis.



In the case of the gaseous acylium ions, ketalization with diols and analogs proceeds by initial acylation at the hydroxyl group, followed by intramolecular proton transfer and HX neutral loss that is most likely assisted by ring-closure with intramolecular nucleophilic substitution (Scheme 10). This novel reaction occurs, therefore, in a way very similar to condensed phase ketalization; also, protection of the acylium ions, in the form of the cyclic “ionic ketals,” against their most characteristic reactions was verified [Moraes, Pimpim, & Eberlin, 1996]. Gas-phase ketalization of a series of O-alkylated ketones with 2-methoxyethanol has also been observed and corroborated via pentaquadrupole MS, whereas protonated ketones undergo mainly proton transfer [Moraes & Eberlin, to appear].

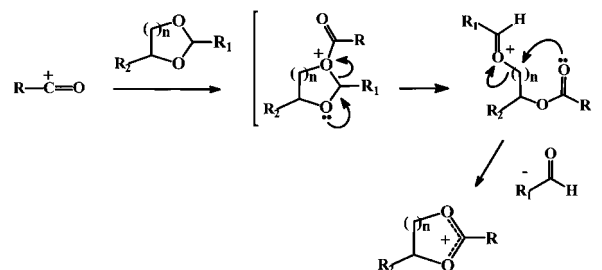
E. Transacetalization with Acylium Ions and Analogs

Transacetalization with a second aldehyde or ketone [Eq. (4)] is also a classic reaction in the condensed phase that is used either to protect or reform the original carbonyl compound. Gas-phase transacetalization with neutral cyclic acetals and ketals has also been shown by pentaquadrupole MS to take place in high yields for a variety of acylium (R—C⁺=O), thioacylium (R—C⁺=S), and the structurally related sulfinyl cations (R—S⁺=O) [Eberlin & Cooks, 1993; Vainiotalo, Moraes, & Eberlin, 1996; Moraes et al., 1997; Moraes & Eberlin, 1997; Gozzo, Sorrilha, & Eberlin, 1996].



In transacetalization with neutral cyclic acetals or ketals (Scheme 11), the “keto” ions displace the “protected” aldehydes and ketones to yield cyclic “ionic ketals”; i.e., 1,3-dioxolanylium ions and derivatives. The reaction occurs most likely via initial O-(or S-)acylation, followed by a ring-opening/ring-reforming process in which the neutral carbonyl compound is eliminated and the cyclic “ionic ketals” are formed. Transacetalization has been shown to occur for a large variety of acylium ions, with no exceptions so far, such that it provides a very general, structurally diagnostic method for the gas-phase characterization of this important class of stable “long-lived” gaseous ions [Eberlin & Cooks, 1993]. Figure 16 illustrates the singular transacetalization and ketalization reactivity of the (CH₃)₂N—CO⁺ acylium ion with 1,3-dioxane and 2-methoxyethanol, respectively. Note in both cases the abundant cyclic “ionic ketal” products of *m/z* 130 and *m/z* 116, respectively.

General transacetalization reactivity [Eq. (5)] and simple dissociation of the products that reforms the original reactant ions, as exemplified by the cyclic “ionic ketal” of CH₃—SO⁺ in Fig. 17(a), have also added to the first evidence collected to establish sulfinyl cations as stable gas-phase species [Gozzo, Sorrilha, & Eberlin, 1996]. An



SCHEME 11.

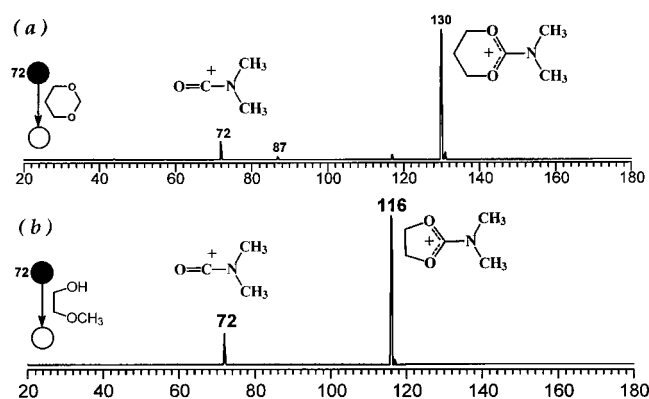


FIGURE 16. Pentaquadrupole double-stage (MS^2) product spectra for ion/molecule reactions of $(CH_3)_2N-CO^+$ with (a) 1,3-dioxane and (b) 2-methoxyethanol. Adapted from References 71 and 72.

interesting exception to the characteristic “precursor ion” reforming dissociation was observed in the pentaquadrupole sequential product spectrum of the transacetalization

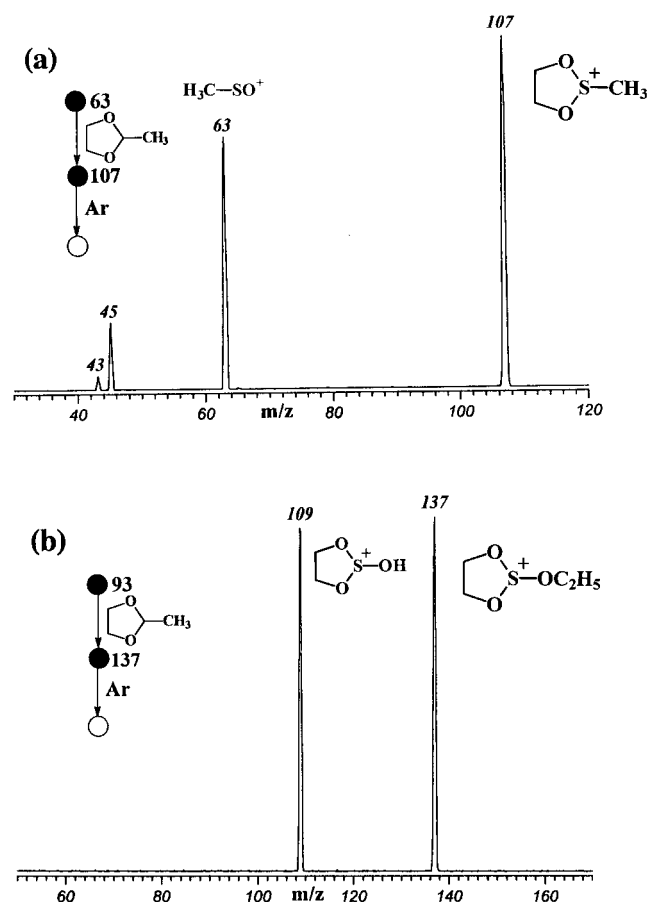


FIGURE 17. Pentaquadrupole triple-stage (MS^3) sequential product spectrum of the cyclic “ionic ketals” arising from ion/molecule reactions of (a) CH_3-SO^+ and (b) $C_2H_5O-S^+=O$ with 2-methyl-1,3-dioxolane. Adapted from Reference 37.

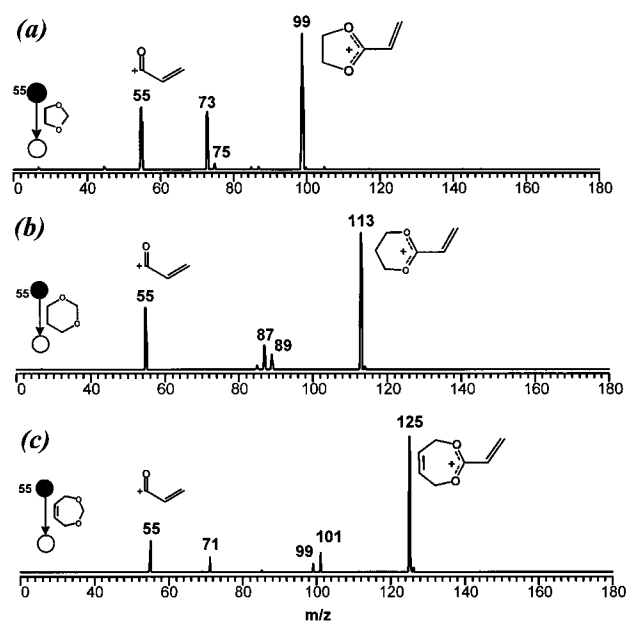
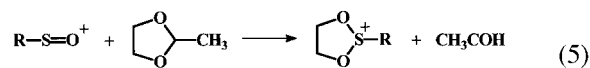


FIGURE 18. Pentaquadrupole double-stage (MS^2) product spectra for ion/molecule reactions of the acylium ion $CH_2=CH-CO^+$ with (a) 1,3-dioxolane, (b) 1,3-dioxane, and (c) 1,3-dioxep-5-ene. Adapted from Reference 71.

product of $C_2H_5O-S^+=O$ [Fig. 17(b)]. Dissociation by loss of (most likely) ethylene (28u), not C_2H_4O (44u), yields the only observed fragment of m/z 109. This singular dissociation, highly favored at the ethyl moiety, was taken as evidence for the covalently bound nature of the product, and for a tendency to preserve the stable cyclic thiodioxolanylium ion structure when favored alternative dissociation processes are available.



Transacetalization with acylium ions was also recently verified to constitute a gas-phase structurally diagnostic test for a variety of 1,3-O,O-cyclic acetals and ketals and some of their *mono*-sulfur and nitrogen analogs [Moraes et al., 1997]. The reaction was found to be very general, and to occur regardless of either the size of the ring (five-, six-, and seven-membered rings were studied) or the nature and position of the substituents, as exemplified in Fig. 18. Substituents of the cyclic acetals and ketals at the 2-position were shown to be eliminated in the course of transacetalization, whereas substituents not at the 2-position remain in the ionic products (Scheme 8). Hence, positional isomers produce different cyclic “ionic ketals” and are easily differentiated. Leinonen & Vainiotalo [1994] also performed transacetalization with acylium ions under acetone and 3-pentanone chemical ionization conditions, and

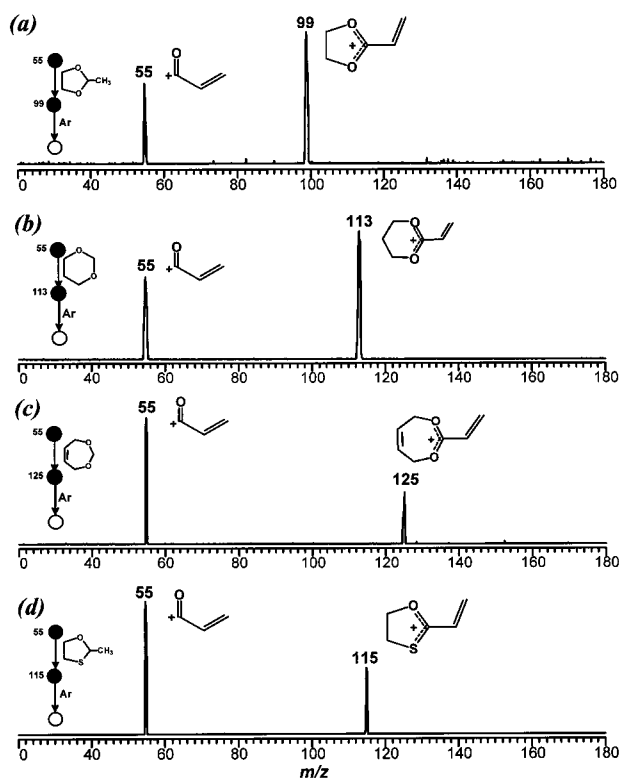


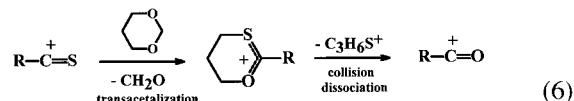
FIGURE 19. Pentaquadrupole triple-stage (MS^3) sequential product spectra of several cyclic “ionic (thio)ketals” formed upon transacetalization of $CH_2=CH-CO^+$ with neutral cyclic acetals. Adapted from References 71 and 72.

the distinction of 1,3-dioxolanes and their *mono*-sulfur analogs was accomplished. Characterization of chemi-ions in flames has also been performed on the basis of these structurally diagnostic reactions [Egsgaard et al., 1996].

Interestingly, pentaquadrupole sequential product scans and comparisons with reference ions show most often that the acylium ions are reformed in high yields upon CID of the cyclic “ionic ketals” (Fig. 19) that are formed either by transacetalization or by direct ketalization; that step is, therefore, equivalent to the reforming hydrolysis of the neutral acetals and ketals in the condensed phase. This simple dissociation chemistry has been amply demonstrated to be a very general characteristic of cyclic ionic ketals. Therefore, transacetalization or ketalization can both be used efficiently for the protection, elimination, trapping, or characterization of acylium ions in the gas phase. These ion/molecule reactions seem also to be very promising as structurally diagnostic tests for a variety of biologically relevant molecules for which acetals and ketal rings or hydroxy, SH, amino, and ether linkages are among the most common functional groups [Moraes et al. 1997].

The case of $CH_3-C^+=S$ shown in Fig. 20 is, however, unique and also quite interesting. Its cyclic “ionic thioketal” does not reform the original reactant ion

($CH_3-C^+=S$) upon CID, but it dissociates exclusively to the oxygen analog $CH_3-C^+=O$ [Fig. 20(b)]. This novel triple stage pentaquadrupole mass spectrometric transacetalization/CID sequence [Eq. (6)] was, therefore, proposed as an efficient MS^3 gas-phase strategy for the conversion of thioacylium ions into acylium ions [Moraes & Eberlin, 1997].



Transacetalization has also been applied with success to differentiate the acetyl cation from the classical set of $C_2H_3O^+$ ions [Eberlin & Cooks, 1993]. The product spectra of the three isomers investigated arising from reactions with 1,3-dioxolane are shown in Fig. 21. The acetyl cation, formed from dissociative EI of methyl acetate in ca. 98% yield, is characterized by the formation of an intense cyclic “ionic ketal” of m/z 87 [Fig. 21(a)]. The product spectrum of O-protonated ketene (actually $CH_2=CH=OD^+$ was used), formed from ethanol-OD, displays mainly the proton (D^+) transfer products of m/z 75 and 76 and the hydride abstraction product of m/z 73 [Fig. 21(b)]. The cyclic oxiranyl cation [Fig. 21(c)] also reacts mainly by proton transfer (m/z 75) and hydride abstraction (m/z 73), whereas formation of the minor transacetalization product ion of m/z 87 and its abundance are completely accounted for by the reaction of ca. 20% of the acetyl cation that is co-generated from 1,3-dichloro-2-propanol [Eberlin, Majumdar, & Cooks, 1992].

F. Transacetalization with Pyridyl Cations

Recently [Carvalho, Eberlin, & Kascheres, 1996; Carvalho et al., to appear], a novel “transacetalization-like” reac-

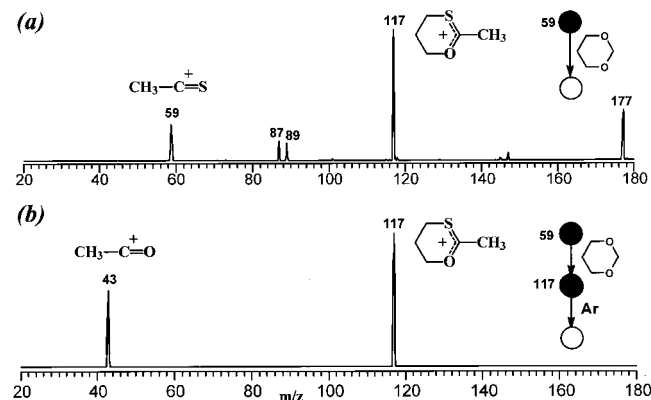


FIGURE 20. Pentaquadrupole double-stage (MS^2) product spectra for ion/molecule reactions of CH_3-CS^+ with 1,3-dioxane and (b) the triple-stage (MS^3) sequential product spectrum of the cyclic “ionic thioketal” of m/z 117. Adapted from Reference 69.

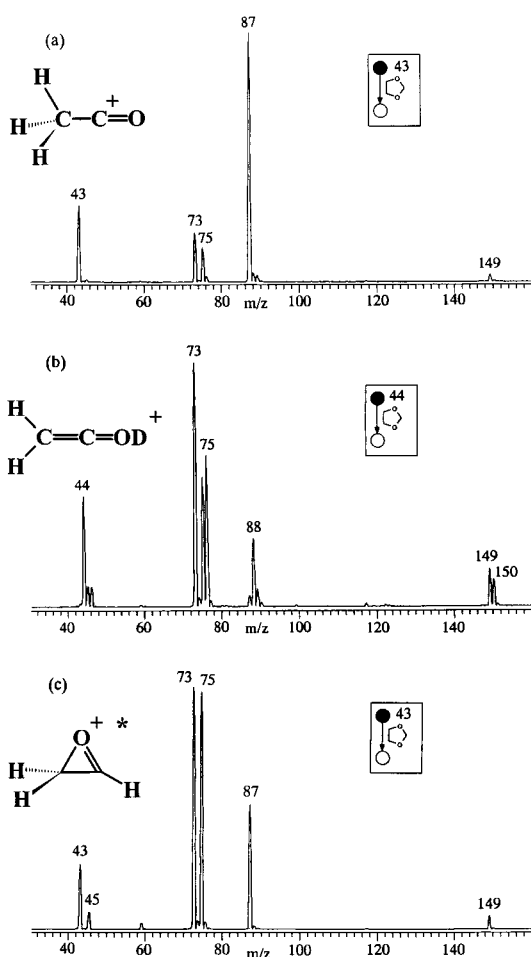
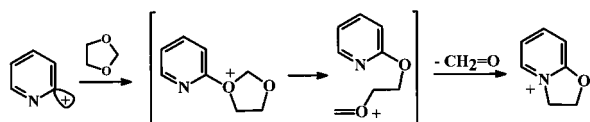


FIGURE 21. Pentaquadrupole double stage (MS^2) product spectra for ion/molecule reactions of three isomeric $C_2H_3O^+$ ions with 1,3-dioxane. Adapted from Reference 20.

tion also has been shown to be useful in distinguishing between isomeric pyridyl and pyrimidyl cations, and thus to allow the determination of ring charge location. For instance, the 2-pyridyl cation, i.e., the 1-aza-benzynium ion [Gozzo et al., to appear] is by far the most reactive, and this reactivity can be rationalized, in view of the mechanism depicted in Scheme 12, as an effect of facile intramolecular displacement proportioned by the *ortho*-pyridine ring nitrogen. A bicyclic pyridinium ion is formed, as evidenced by triple-stage pentaquadrupole MS and as predicted by *ab initio* calculations.



SCHEME 12.

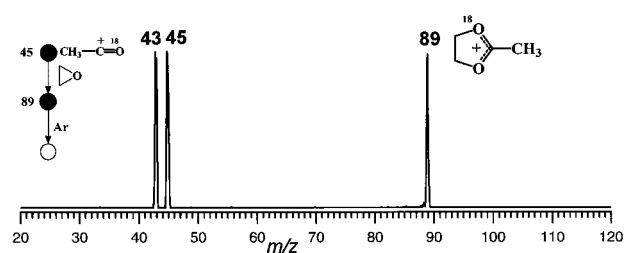


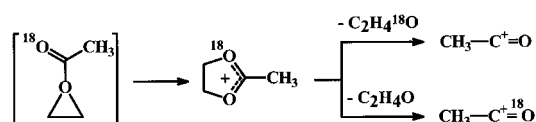
FIGURE 22. Pentaquadrupole triple-stage (MS^3) sequential product spectrum of the ^{18}O -cyclic "ionic ketal" formed upon acylation of ethylene oxide with $CH_3-C^{18}=O$ followed by ring expansion.

G. Ring Expansion of Epoxides via Acylation

Still more recently [Morales & Eberlin, to appear], another novel gas-phase reaction for acylium ions and analogs was observed and validated by pentaquadrupole MS. In reactions with several epoxides, abundant adducts were formed. *Ab initio* calculations indicated that the primary adducts should not be stable, because isomerization by ring-expansion took place without any considerable activation barrier during geometry optimization. The same class of five-membered cyclic "ionic ketals," which are formed upon direct ketalization or transacetalization with acylium ions (see Schemes 10 and 11), were, therefore, predicted by the calculations as the most likely products. Because the triple-stage spectra show that the adducts dissociate upon collision activation to reform exclusively the reactant acylium ion, it could not be verified whether three- to five-ring expansion has indeed taken place. ^{18}O labeling, however, shows that the labeled and the unlabeled acylium ion both occur when dissociating the $CH_3-C^{18}O$ /ethylene oxide adduct (Fig. 22); that result can only be explained by assuming the ring-expansion oxygen-scrambling mechanism depicted in Scheme 13.

H. Ionized Methylene (CH_2^+) and Methyne Cation (CH^+) Transfer

It has long been known mainly from ICR and CI studies [Hammerum, 1988] that the $^+CH_2-O-CH_2$ α -dionone ion transfers CH_2^+ and CH^+ to a variety of compounds in the gas phase. This reaction was investigated by pentaquadrupole MS [Gozzo & Eberlin, 1995]. Ionized methylene (CH_2^+) transfer was observed to occur extensively to a



SCHEME 13.

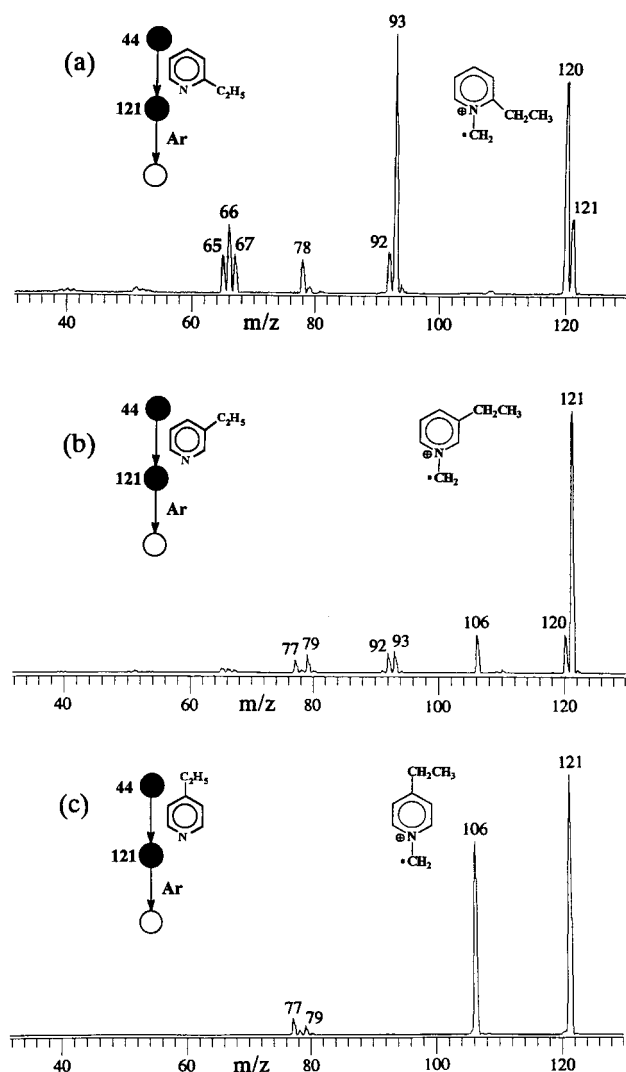


FIGURE 23. Pentaquadrupole triple-stage (MS^3) sequential product spectra of the ionized methylene transfer products of $^+CH_2-O-CH_2$ to the three isomeric ethyl pyridines. Reproduced with permission from Reference 35.

series of neutral pyridines under the quadrupole collision cell reaction conditions, whereas pentaquadrupole sequential-product scans proved that transfer takes place to the ring nitrogen. Such scans applied to the CH_2^+ transfer products of the three isomeric ethyl pyridines show that each possesses a remarkably different dissociation chemistry (Fig. 23). Thus, this derivatization/dissociation MS^3 sequence is promising for the differentiation of isomeric alkylpyridines and analogs. Methyne cation (CH^+) transfer, on the other hand, was the major reaction observed with five-membered heterocyclic furan, thiophene, pyrrole (Fig. 24), and methylpyrrole. Initial attack occurs most likely at the ring followed by an interesting ring-expansion process (Scheme 14, $X=O, S, NH, NHCH_3$). For instance,

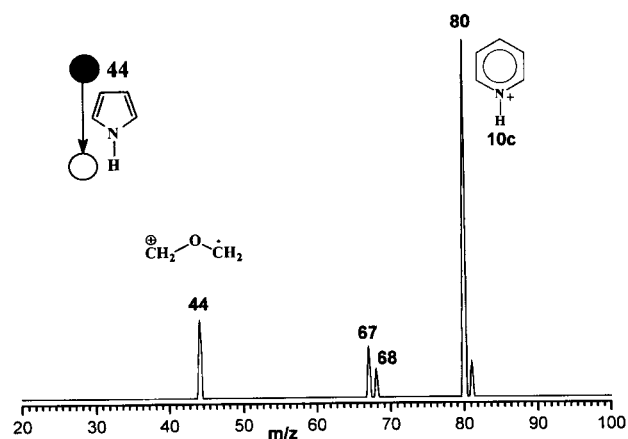
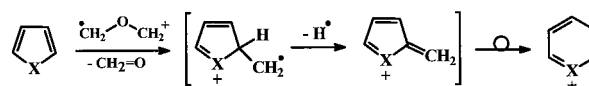


FIGURE 24. Pentaquadrupole double-stage (MS^2) product spectra for ion/molecule reactions of $^+CH_2-O-CH_2$ (m/z 44) with pyrrole. Reproduced with permission from Reference 42.

formation of protonated pyridine upon CH^+ transfer to pyrrole that proceeds via five- to six-membered ring expansion has been supported by MS^3 scans and comparison with the authentic reference ion; i.e., protonated pyridine (Fig. 25).

I. Making and Characterizing Ions “On-Line”: Radical Coupling Reaction with O_2 .

A recent study of *eleven* isomers of $PyC_2H_5^+$ composition [Sorrilha et al., 1996] provided a remarkable illustration of the way in which pentaquadrupole MS can contribute to the generation and particularly to the “on-line” characterization of gas-phase ionic species. The isomers were generated by either the conventional way, that is by the direct EI of selected neutral precursors, or via ion/molecule reactions or sequences of CI ion/molecule reactions followed by CID. Characterization was achieved by either comparing their low-energy CID behavior (Fig. 26) or chemical reactivity in radical-coupling reactions with the O_2 molecule (see Fig. 9). In this study, an intermediate-product domain three-dimensional spectrum was presented and used to display in a single 3-D plot all of the products of the Q1-mass-selected $^+CH_2-O-CH_2$ ions of m/z 44 with 2-methyl pyridine, each associated with its corresponding CID fragments (Fig. 27). *Extractions* from the 3D spectrum along the Q5 axis (fixed Q3 masses) were used to obtain 2D sequential product ion spectra [Fig. 27(b)], whereas reconstruction of the product ion spectrum



SCHEME 14.

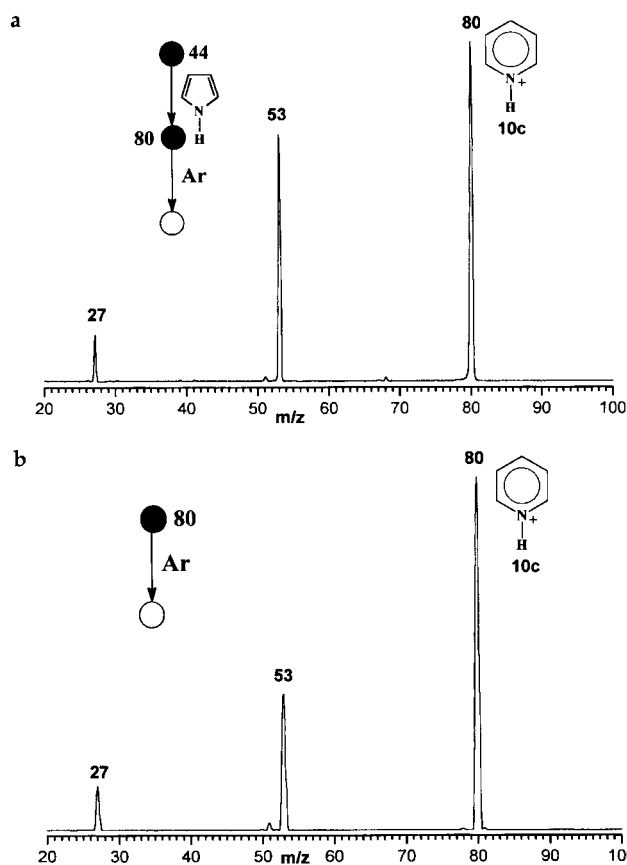


FIGURE 25. (a) Pentaquadrupole triple-stage (MS^3) sequential product spectrum of the net CH^+ transfer product to pyrrole of m/z 80 and (b) double-stage (MS^2) spectrum of the authentic ion; i.e., protonated pyridine. Reproduced with permission from Reference 35.

[Fig. 27(c)] was performed by *projection* of the 3D spectrum towards the Q5 axis.

J. Electrophilic Aromatic Cl^+ (and Br^+) Addition and CO^{++} Substitution

In spite of the importance of electrophilic aromatic substitution in solution, halogen cation addition in gas-phase MS environments has received little attention because of the lack of appropriate halogenating species. Using pentaquadrupole MS, however, Kotiaho et al. [1993] showed that chlorination (Cl^+ addition or transfer) of aromatic compounds can be performed via low-energy ion/molecule reactions with appropriate reactant ions, and that the “mono-solvated” Cl^+ ion, i.e., protonated chloramine (NH_3Cl^+) and the acylium ion $Cl-C^+=O$ were both useful. The “solvents” CO and NH_3 constitute good leaving groups that help by promoting internal energy loss from the collision complex, thus stabilizing the nascent Cl^+ addition products. CO^{++} substitution also occurs for $Cl-C^+=O$, whereas a unique reaction, NO_2^+ replacement

by Cl^+ , occurred in reactions with nitrobenzene. In contrast to the reactivity of the “solvated” ions, reactions with the “bare” Cl^+ ion failed to provide Cl^+ addition; that ion reacts exclusively by charge exchange or, as shown in a related study [Bortolini, Yang, & Cooks, 1993], by quite exothermic Cl^+ addition ($M + Cl^+$) that leads to rapid dissociation to M^{++} by Cl^+ loss. Scheme 15 summarizes the main results for aniline. Reaction sites were determined in most cases with the help of triple-stage pentaquadrupole sequential-product spectra and by making comparisons with the double-stage product spectra of reference

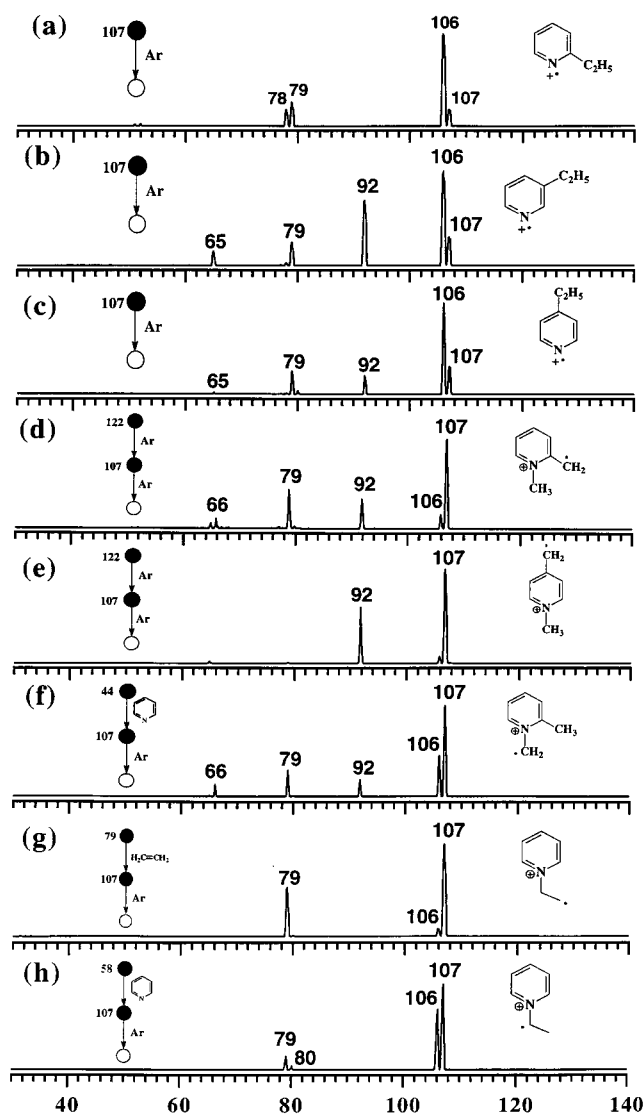


FIGURE 26. Pentaquadrupole double-stage product spectra (a)–(c) and triple-stage (MS^3) sequential product spectrum (d)–(h) of several isomeric ions of $PyC_2H_5^+$ composition. The spectra of the 3-isomer and the 3- and 4-isomers closely resemble those shown in Figs. (e) and (f), respectively, and are not shown. Reproduced with permission from Reference 88.

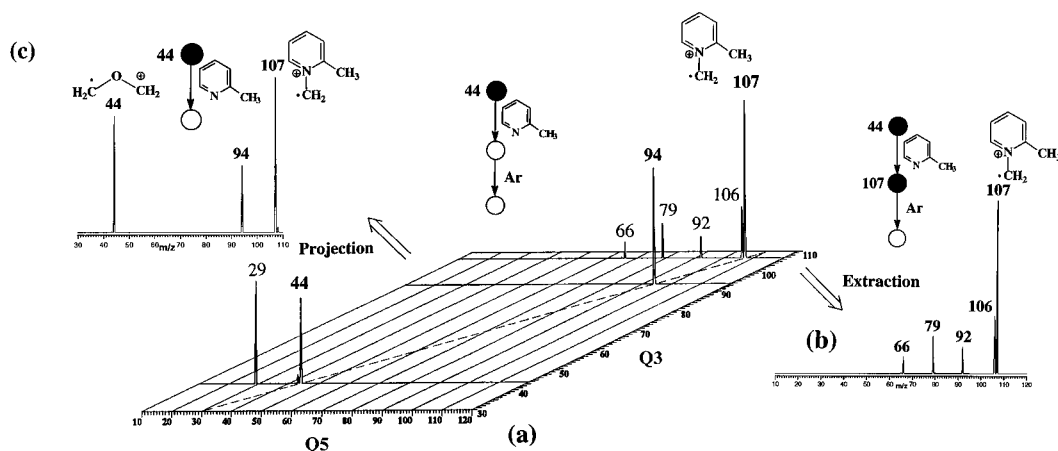


FIGURE 27. (a) Pentaquadrupole 3D triple-stage (MS^3) intermediate-product domain spectrum for ion/molecule reactions of ${}^+\text{CH}_2\text{—O—CH}_2$ (m/z 44) with 2-methylpyridine. (b) Extracted 2D triple-stage sequential product ion spectrum of the CH_2^+ transfer product of m/z 107, and (c) reconstructed (by projection toward the Q3 axis) 2D double-stage product spectrum. Reproduced with permission from Reference 88.

ions. The reaction sites of aniline and anisole for Cl^+ addition were determined to be preferentially the *para*-ring carbons, whereas Cl^+ addition occurred mainly at the β -carbon of the vinyl substituent in styrene. For aniline, CO^+ substitution was determined to occur at the nitrogen and the *para*-ring carbon.

The latter study was extended to investigate by pentaquadrupole MS, the addition of Br^+ to benzene and to mono-substituted benzenes, using $\text{Br—C}^+=\text{O}$ and $\text{CH}_3\text{NH}_2\text{Br}^+$ as the reagents [Bortolini, Yang, & Cooks, 1993]. Br^+ addition was found to occur readily, especially for $\text{Br—C}^+=\text{O}$, and at ratios that correlate well with Brown's Hammett-type substituent parameters σ^+ . Additionally, much greater, i.e., less negative reactivity parameters (ρ), than those observed in solution were obtained; thus, Br^+ displays an increased reactivity in the "absence" of solvent (note that in fact what could be considered "mono-solvated" Br^+ ions were used). The triple-stage pentaquadrupole spectra of the $(\text{M} + \text{Br})^+$ products show exclusive dissociation to M^+ and Cl^+ ; that dissociation

suggests that the electrophilic addition reaction proceeds via a σ -complex to the ring, and that the M^+ ions observed in the product spectra arise likely not from charge-exchange, but from "reaction-induced" dissociation of the nascent $(\text{M} + \text{Br})^+$ product ions.

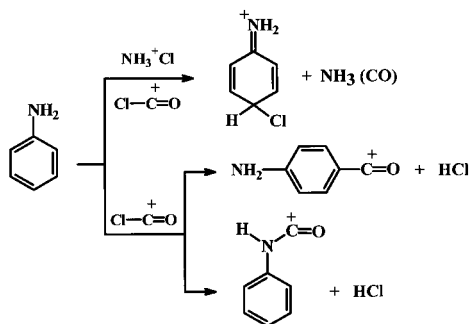
K. CX^+ ($\text{X}=\text{Cl}, \text{Br}, \text{I}$) Transfer to Aromatic Compounds

Carbocations are key intermediates in a number of reactions of interest in condensed phase chemistry, and their intrinsic reactivity has been studied in the gas phase via several mass spectrometric techniques. The reaction of a variety of halogenated carbocations with aromatic compounds was recently investigated by pentaquadrupole MS [Pimpim, Sorilha, & Eberlin, 1996]. CX^+ ($\text{X}=\text{Cl}, \text{Br}, \text{I}$) transfer is a common reaction and the relative reactivity of the ions and the extent of competitive reactions have been evaluated. For instance, in reactions of CHClBr^+ with benzene, CCl^+ transfer occurs to a greater extent than CBr^+ transfer, whereas practically no CH^+ transfer is observed. Structural assignments of reaction products have been made with the help of triple-stage pentaquadrupole scans.

L. Oxygen Atom Transfer

1. From Ozone to Ionized Pyridines, Pyrimidine, Methyl Halides, and Halogen Cations

Very recently [Mendes et al., to appear], pentaquadrupole MS has been used to study the gas-phase chemistry of ionized species with ozone (O_3), which is an essential



SCHEME 15.

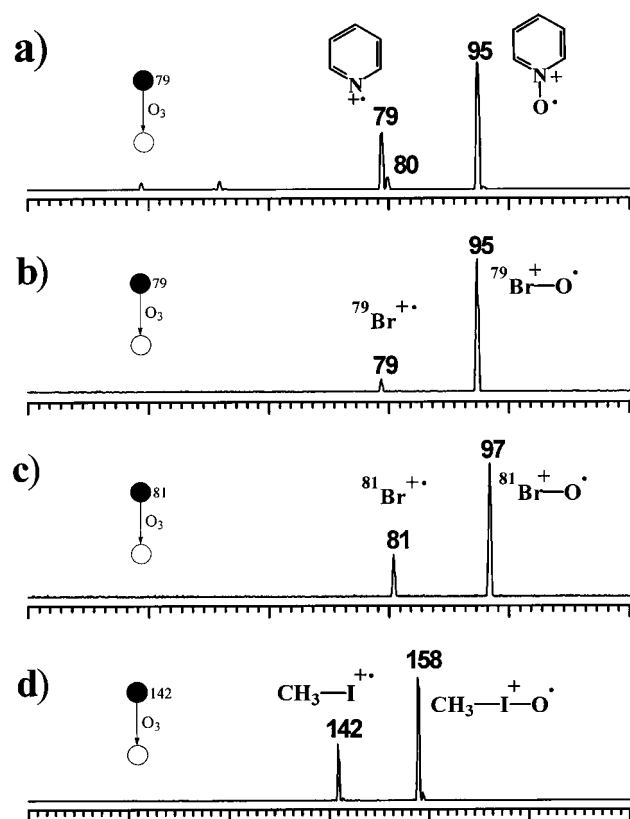
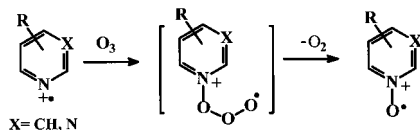


FIGURE 28. Pentaquadrupole double-stage (MS^2) product spectra for ion/molecule reactions of (a) ionized pyridine, (b) $^{79}\text{Br}^+$, (c) $^{81}\text{Br}^+$, and (d) ionized methyl iodide with ozone. Adapted from Reference 65.

molecule that plays the key role of an ultraviolet light screen in the upper atmosphere and in the condensed phase as a strong oxidizing agent. A variety of ion/molecule reactions of mass-selected ionic species with neutral ozone were performed. As exemplified in Fig. 28, ionized pyridines and Pyrimidine (Py^+), ionized methylhalogenides (RX^+), and the ionized halogen atoms (X^+ , except F^+) were observed to react with neutral ozone by a novel oxygen atom transfer reaction that leads to their corresponding oxide derivatives; i.e., the $\text{Py}^+-\text{O}^\bullet$ (Scheme 16), $\text{RX}^+-\text{O}^\bullet$ and $\text{X}^+-\text{O}^\bullet$ ions. Structural characterization of the products was accomplished via MS^3 experiments, which permitted an examination of their dissociation chemistry and, when possible, comparison with those of reference ions. It was also interesting to note that oxy-



SCHEME 16.

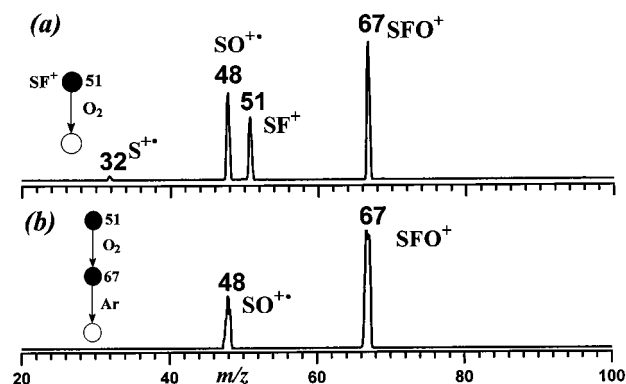


FIGURE 29. Pentaquadrupole double-stage (MS^2) product spectra for ion/molecule reactions of SF^+ with O_2 and (b) triple-stage (MS^3) sequential product spectra of the oxygen atom transfer product SFO^+ .

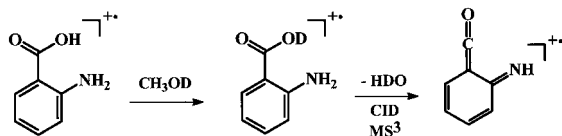
gen atom transfer is not observed for the “reverse” reactions (i.e., those of the ionized ozone with the corresponding neutrals), where electron transfer dominates. The possibility that these oxygen atom transfer reactions can contribute to ozone depletion should, therefore, be investigated. Additionally, these novel reactions provide a ready means for the gas-phase generation of a series of ionized oxides, some of which are difficult to access, such as $\text{RX}^+-\text{O}^\bullet$ and $\text{X}^+-\text{O}^\bullet$.

2. From O_2 , CO_2 , and N_2O to SF_n^+ Ions

Oxygen atom transfer from several neutral molecules to SF_n^+ ions has also been observed and corroborated via pentaquadrupole MS [Eberlin et al., to appear]. The set of SF_n^+ ions ($n = 0, 5$) were reacted with a variety of neutrals. SF_2^+ , S^+ , and especially SF^+ were found as the most reactive species, and oxygen atom transfer occurs readily, especially with O_2 , CO_2 , and N_2O . Figure 29(a) shows the products that arise from the reactions of SF^+ with O_2 . Note the O-transfer products to $\text{SF}^+(\text{OSF}^+)$ and $\text{S}^+(\text{SO}^+)$; the S^+ ion is formed by the dissociation of SF^+ . Evidence for OSF^+ formation is provided by its sequential product spectrum [Fig. 29(b)], which shows main dissociation to SO^+ .

M. Hydrogen/Deuterium (H/D) Exchange

Very specific structural information can be provided by H/D isotope exchange ion/molecule reactions, which are useful in determining the number of active or acidic hydrogens that are present in certain ionized molecules. Ranainghe, Cooks, & Sethis [1992] observed, for instance, in reactions of a variety of ionized and protonated aromatic compounds, that ND_3 allows the exchange of all active hydrogens, and thus provides a count of the total number



SCHEME 17.

of active hydrogens present in the analyte. On the other hand, CH₃OD exchanges only specific types of active hydrogens, such as phenolic and carboxylic hydrogens, without exchanging amino hydrogens. This selectivity assists in the identification and enumeration of the different types of active hydrogens present in polyfunctional compounds. A triple-stage pentaquadrupole mass scan was used to help to elucidate the exchange process. The sequential product spectrum of the *d*₁-M⁺⁺ molecular ion of anthranilic acid shows a major dissociation to *m/z* 119 by HDO loss (Scheme 17), thus providing evidence that the hydrogen exchange with CH₃OD involves only the hydrogen of the carboxylic group (Scheme 17).

N. Ionic Dimer Formation with Pyridines

1. Ion Affinities and Steric Parameters

The relative gas-phase cation affinities of a group of substituted pyridine have been estimated by the *Cooks' kinetic method* [Cooks et al., 1994], using pentaquadrupole MS [Eberlin et al., 1994; Yang et al., 1995; Wong et al., 1997; Yang et al., 1995; Yang et al., 1996; Ma et al., to appear]. The cation-bound dimers were generated in ion/molecule reactions of mass-selected ions under controlled conditions (appropriate collision energy and partial vapor pressures of the neutral reactants) with a mixture of two pyridines in the first reaction quadrupole (Q2). Figure 30 shows a typical example for the reaction of Cl—C⁺=O

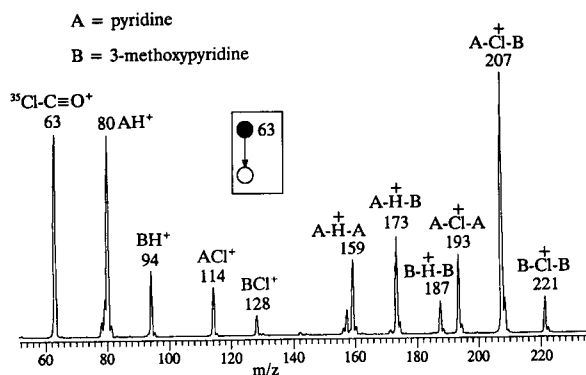


FIGURE 30. Pentaquadrupole double-stage (MS²) product spectra for ion/molecule reactions of ³⁵Cl—C⁺=O with a mixture of pyridine and 2-methoxy pyridine. Reproduced with permission from Reference 21.

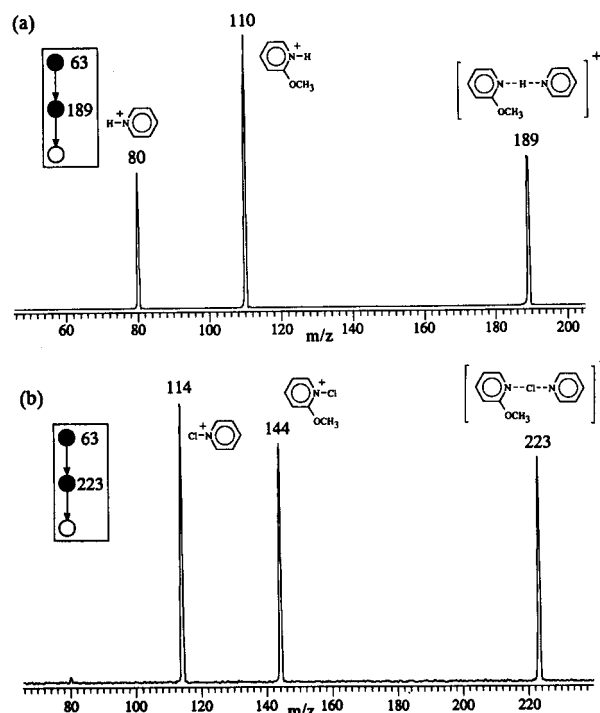


FIGURE 31. Pentaquadrupole triple-stage (MS³) sequential product spectra of the two “asymmetric” (a) H⁺-bound dimer and (b) ³⁵Cl⁺-bound dimer. Reproduced with permission from Reference 21.

with a mixture of pyridine and 2-methoxy pyridine [Eberlin et al., 1994]. Note the typical mixture of products that includes the two protonated pyridines (AH⁺ and BH⁺), the two chlorinated pyridines (ACl⁺ and BCl⁺), the two symmetrical proton- (A-H⁺-A and B-H⁺-B) and Cl⁺-bound dimers (A-Cl⁺-A and B-Cl⁺-B) and, most interestingly, the unsymmetrical proton- (A-H⁺-B) and Cl⁺-bound dimers (A-Cl⁺-B). The simultaneous generation, further mass-selection of each of these unsymmetrical dimers, and “on-line” CID in q4 under the very same experimental QQQQ conditions (Fig. 31) have allowed for the first time the ordering and estimation of an interesting series of ion affinities through an application of the *kinetic method*.

In these studies, it has been considered quite reasonably that the same electronic effects known to affect proton affinities are also likely to affect other ion affinities, and that, if these effects parallel each other, then the same order of proton and ion affinity is to be expected. This hypothesis was tested and found to be perfectly valid for “unhindered” pyridines (Fig. 32). However, “hindered” pyridines, which bear electron-donating groups at the 2-position, show “lower than expected” affinities; that effect is attributed to steric hindrance because the effect increases with the bulkiness of the 2-substituent and the complexing ion, as well as with the ion affinity of the pyridines. This relationship follows because the greater

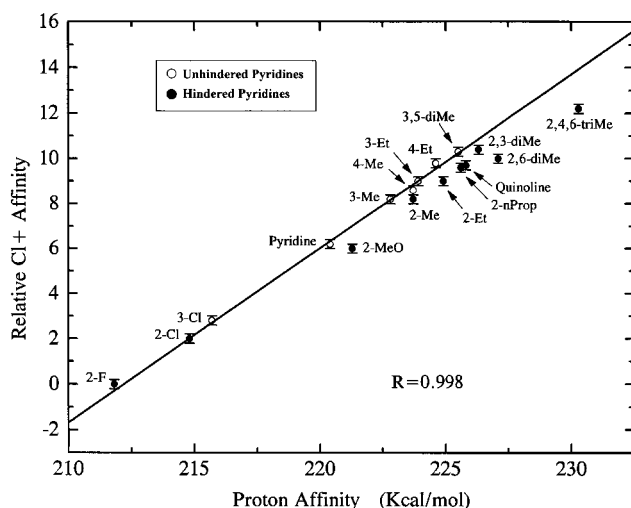


FIGURE 32. Plot of the experimental relative Cl^+ affinities vs. H^+ affinities of a series of pyridines. Note the very good correlation for the unhindered pyridines ($R = 0.998$), whereas most *ortho*-pyridines display lower than expected Cl^+ affinities. Adapted from Reference 21.

size of the ion and the higher ion affinity of the pyridine shorten the bond lengths and intensify the intramolecular repulsions. Steric hindrance was not only observed to reduce the observed values of ion affinity, but also, in some cases, to cause inversions when compared to the PA order (Fig. 31). Owing to the very small size of the proton, steric effects are expected to be negligible for the proton-bound dimers; therefore, the often very difficult task of separating steric from electronic effects has been adequately performed in these studies. Electronic effects are separated from steric effects by comparing the dissociation of H^+ - and ion-bound dimers of pyridines, which, as already mentioned, are formed and dissociated under the very same QqQqQ experimental conditions. The pentaquadrupole allows an almost perfect comparison, because the only change made to acquire both spectra was the selection of the appropriate ion in Q3. From these results, gas-phase steric parameters S^k have been defined and compared to the S^0 steric parameters that were obtained from solution kinetic measurements.

This same approach applied to Cl^+ has been successfully extended to access the gas-phase affinities of pyridines to a variety of other ions; i.e., Br^+ and I^+ [Eberlin et al., 1994], OCNCO^+ [Yang et al., 1995], SF_3^+ [Wong et al., 1997], CN^+ [Yang et al., 1995], SiCl_n^+ [Yang et al., 1996], PCl_2^+ [Ma et al., 1977], and Fe^+ [Ma et al., 1996]. As a natural result of comparing ion affinities to the same set of neutrals, the quantitative estimates of ion-neutral bond energies and ion bulkiness should be straightforward.

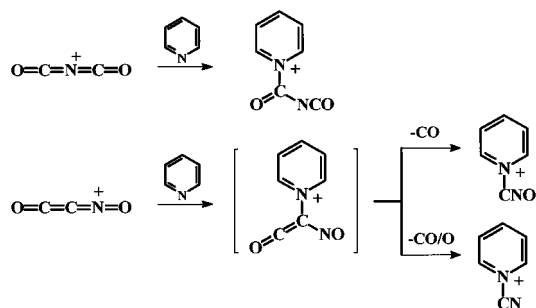
2. Gas-Phase Agostic Bonding

Very recently, the first evidence for gas phase *agostic* bonding has also emerged from the study of SiCl_3^+ and

SiCl^+ [Yang et al., 1996]. SiCl_3^+ behaves analogously to other cations studied, where steric effects are observed for the *ortho*-substituted pyridines. However, an *inverse* steric effect was observed for SiCl^+ with *ortho*-substituted pyridines. The anomalous behavior of SiCl^+ is believed to be due to the intramolecular auxiliary bonding between the hydrogen of the methyl group and the central silicon atom in the form of *agostic* three-center two-electron bonding $\text{Si}-\text{H}-\text{C}$. The existence of auxiliary bonding is supported by theoretical calculations for the SF_3^+ case, where the eclipsed form of the 2-methylpyridine/ SF_3^+ adduct [Wong et al., 1997] is ca. 0.8 kcal/mol more stable than the staggered conformer. In the eclipsed form, the SF_3 group was predicted to adopt an interesting geometry that better exposes the sulfur atom, thus allowing a more efficient interaction with the hydrogen of the methyl group. The charge distribution of the eclipsed conformation shows that the charge on the bonding hydrogen $\text{S}-\text{H}-\text{C}$ (+0.07) is considerably lower than that of the other two hydrogens (+0.14); that difference was taken as an indication of auxiliary bonding.

O. Stable and Unstable Adducts with Pyridine ($\text{OCNCO}^+/\text{OCCNO}^+$)

Pentaquadrupole MS and ion/molecule reactions with pyridines have also been applied to characterize and to study the gas-phase chemistry of an interesting pair of ionic isomers; that is, the heterocumulene cations OCNCO^+ and OCCNO^+ [Carvalho et al., 1997; Carvalho et al., 1997]. Although both of these acylium ions react readily and similarly with 2-methyl-1,3-dioxolane by transacetalization, they show quite a distinct reactivity with the strong nucleophile pyridine (Scheme 18). OCNCO^+ forms a very abundant and stable pyridine adduct, which is shown by MS^3 to dissociate upon collision exclusively to the original reactant ion. The OCCNO^+ isomer, on the contrary, does not form a stable adduct with pyridine, and the main products are $\text{Py}-\text{CNO}^+$ and $\text{Py}-\text{CN}^+$, formed, respectively, by CO and CO/O loss from the unstable adduct, i.e., the



SCHEME 18.

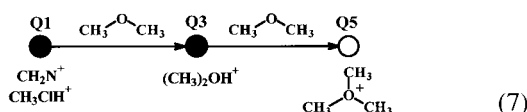
ion/molecule complex. Triple-stage spectra of the ionic products are in agreement with the structures depicted in Scheme 18.

P. Sites of Alkylation

By applying pentaquadrupole scans and by making comparison with reference ions, Dolnitowski et al. [1990] investigated the sites of methylation on protonated acetaldehyde that occurs in gas-phase reactions with methanol. Triple-stage pentaquadrupole scans permitted gas-phase synthesis and subsequent CID of two different deuterium-labeled variants of the methylated acetaldehyde. Thus, the sequential product spectra of $\text{CH}_3\text{—O}^+\text{=CH—CH}_3$ (synthesized in Q2 by reactions of CH_3OH_2^+ with CH_3COH), $\text{CD}_3\text{—O}^+\text{=CH—CH}_3$ (CD_3OD_2^+ with CH_3COH), and $\text{CH}_3\text{—O}^+\text{=CD—CD}_3$ (CH_3OH_2^+ with CD_3COD) were compared. Rationalization of the dissociation mechanism and the agreement of the observed mass shifts with those expected for each of the labeled ions provides confirmatory evidence for O-methylation.

Q. Mechanisms of Ion Formation

Two studies performed by Tedder & Walker [1991]; and by Hollis et al. [1991] have employed pentaquadrupole MS to interrogate the mechanism of ion formation in ion/molecule reaction processes. From the results obtained, reaction schemes invoking $\text{S}_{\text{N}}2$ nucleophilic addition/elimination steps for the formation of the trimethyl oxonium ion $\text{O}^+\text{—(CH}_3)_3$ from methanol [Tedder & Walker, 1991] and the $\text{CH}_3\text{—X}^+\text{—CH}_3$ from methyl halides [Hollis et al., 1991] were proposed. A triple-stage pentaquadrupole experiment [Eq. (7)] was used to show that trimethyl oxonium ions $\text{O}^+\text{—(CH}_3)_3$ are formed in reactions of neutral dimethyl ether with protonated dimethyl ether, which was formed either by proton transfer reactions with CH_3ClH^+ or CH_2N^+ . In the case of CH_3ClH^+ , direct methylation from the reactant ion could not be excluded as an alternative to $\text{O}^+\text{—(CH}_3)_3$ formation.

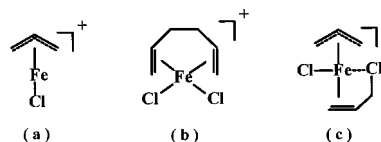


R. Metal Ion Chemistry

Pentaquadrupole MS has also been utilized in the investigation of ion/molecule reactions of metal cations in the gas phase. The interest in these experiments [Eller & Schwartz, 1991] comes from the possibility of generating and examining the reactive intermediate species that were

postulated for condensed-phase organometallic reactions. Sablier et al. [Sablier et al., 1994; Sablier, 1994] studied reactions of bare, first-row transition-metal cations (M^+) with two CN^+ precursors; that is, cyanogen bromide (BrCN) and cyanogen iodide (ICN). MX^+ and the new ionic species MCN^+ were found to be the main ionic products, whereas secondary reactions especially in the case of ICN afforded a variety of other products such as MCNI^+ , MI_2^+ , and MCNI_2^+ . Summation of product intensities gave the following order of gas-phase reactivity: $\text{Sc}^+ \gg \text{Ti}^+, \text{V}^+ > \text{Mn}^+, \text{Fe}^+, \text{Co}^+ > \text{Cr}^+, \text{Ni}^+, \text{Zn}^+, \text{Cu}^+$, whereas in respect to the neutral reactants ICN was found to be much more reactive than BrCN . Structural characterization of the reaction products was attempted by CID performed via sequential product scans. An MS^3 scan showed that ScCN^+ dissociates exclusively to Sc^+ to a relatively modest extent; that result is expected from thermochemical considerations, and indicates a fairly strong $\text{Sc}^+\text{—CN}$ bond.

Mestdagh and Rolando [1989] employed pentaquadrupole MS to investigate the reactions of $\text{Fe}(\text{CO})_n^+$ ($n = 0\text{--}5$) ions with allyl chloride. CID of the Fe^+ adduct ($\text{FeC}_3\text{H}_5\text{Cl}^+$) performed via a triple-stage sequential product scan shows dissociation by neutral loss of C_3H_5 and FeCl ; that dissociation contrasts sharply with the simple propene loss dissociation displayed by the analogous (Fe-propene) $^+$ ion. Those data provide evidence for the insertion complex **a** (see below). Multiple collision conditions lead to secondary products such as $\text{FeC}_6\text{H}_{10}\text{Cl}_2^+$, and its dissociation to form C_6H_{10} indicates the occurrence of a new type of ‘‘ Fe^+ -catalyzed’’ C—C bond formation reaction between the two C_3 units. A subsequent ligand-exchange reaction of the q2 product ion $\text{FeC}_6\text{H}_{10}\text{Cl}_2^+$ with acetonitrile (and $\text{CD}_3\text{—CN}$) was performed in q4. The occurrence of a fast allyl chloride and two slow FeCl_2 and C_6H_{10} replacement reactions provide evidence for a $\text{FeC}_6\text{H}_{10}\text{Cl}_2^+$ ion mixture composed of ca. 40% of **b** and ca. 60% of **c**.



V. CONCLUSIONS

Pentaquadrupole mass spectrometers display a variety of outstanding features and advantages that make them most suitable laboratories for studies of ion/molecule reactions in the gas phase. Most of the desired steps in these studies, that is, ion production, purification via mass selection, reaction at controlled conditions of energy input, concen-

tration and time, identification, quantitation, and characterization of the ionic products via either their dissociation or chemical reactivity, are performed "on-line" and within a very narrow time window. Pentaquadrupoles are remarkably stable, and conditions can be easily reproduced over long periods. Additionally, the multiple-stage multidimensional data can be readily collected in a variety of forms, from which overall display of results and specific mechanistic and structural information can be accessed. Triple-stage pentaquadrupole MS, although still in its infancy, is undergoing vigorous development. Its applications are increasingly to the study of ion/molecule reactions, a field that by providing insights into structure and reactivity of gaseous ions is naturally placed at the center of attention in mass spectrometry. Many successful examples of the application of pentaquadrupole (QqQqQ) MS to the study of gas-phase ion/molecule reactions have been reported, and it is clear that many more achievements lie ahead as this promising technique develops.

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