Some Novel Ion–Molecule Chemistry within van der Waals Clusters

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Introduction

A subject of considerable scientific interest in recent years has been the study of van der Waals clusters (i.e., complexes of atoms or molecules weakly bound to each other).[1,2] The study of a specific chemical reaction within a cluster[3–10] is especially intriguing since it is possible to directly observe how chemical reactivity changes as a function of stepwise solvation by simply monitoring the change in product yield as a function of cluster size. In addition to the intrinsic interest in reactions within clusters, this work can also aid in understanding the factors that govern reactions in solution but are absent in gas-phase processes.

The field of ion–molecule chemistry is particularly suitable, since mass spectrometry has proven to be such a powerful tool in the investigation of van der Waals clusters. One of the most thoroughly examined reactions is the gas-phase ion–molecule reaction of a cation with its neutral self forming a protonated cation. This protonation reaction[11,12] occurs for a wide variety of molecules and is observed in most cases to be highly exoergic with a large rate constant and little or no activation barrier.

$$M + M^+ \rightarrow MH^+ + \text{fragment} \qquad (1)$$

This facile ion–molecule reaction has also been observed to occur directly within van der Waals clusters:[13–26]

$$M_{n-2}\{M+M^+\} \rightarrow M_{n-2}[MH^+] + \text{fragment} \qquad (2)$$

where M = H_2O,[13] NH_3,[14,15] RCOR,[16] ROH,[17] and ROR[18] and R = CH_3. The molecular cluster ion mass spectrum is typically dominated then by the appearance of protonated product cluster ions generated from a parent cluster ion by reaction 2. Note that for clusters, an added complication arises in that monomer evaporation from the cluster ion can occur. Hence, in general, the protonated cluster ion, designated M_mH^+, is generated from a parent ion M_n^+ where $n > m$.[27]

The experiment, in its simplest form, consists of generating a beam of neutral van der Waals clusters, via a conventional supersonic expansion. This beam is then directed into a stardard mass spectrometer, where a tiny fraction of the clusters are ionized via electron-impact ionization, and subsequently mass analyzed. The molecular beam apparatus that we employ at SUNY/Buffalo consists of an intense Campargue-type cluster beam source coupled with a quadrupole mass spectrometer and has been described previously.[28,29]

As shown schematically in Figure 1, the cation within the cluster is rapidly generated by an inelastic interaction with an energetic electron (20–100 eV energy). The time for this ionization step is small, on the order

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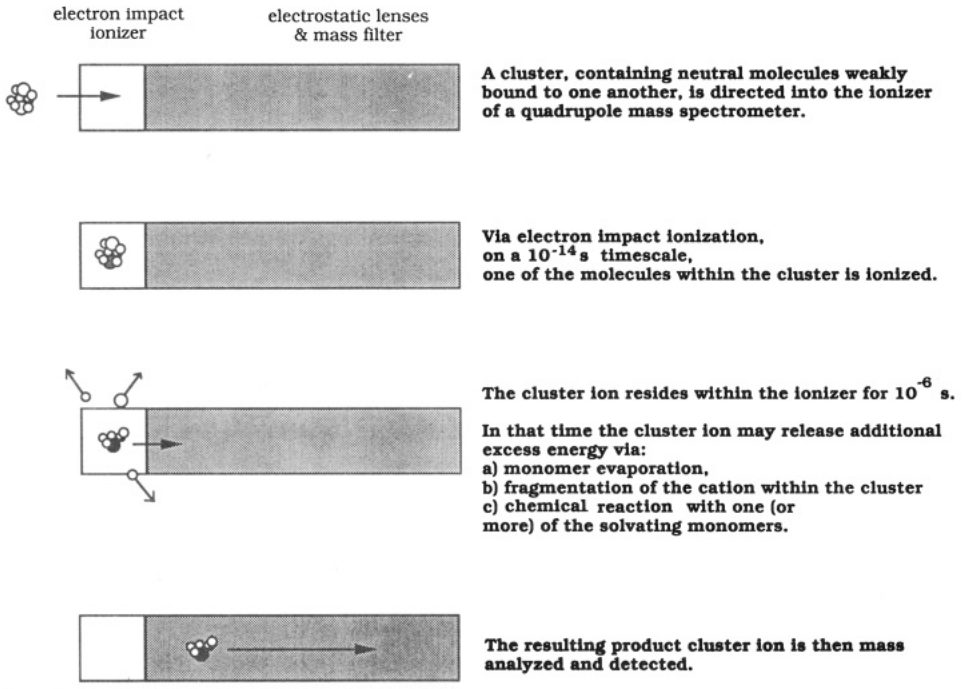

Figure 1. Schematic of experiment.

of 10^{-14} s. However, it will take microseconds before the cluster ion physically migrates out of the ionizer of the mass spectrometer and is actually mass selected and detected. On such a lengthy time scale, the cation within the cluster has ample opportunity to rid itself of the excess energy deposited via the electron-impact ionization. This cooling of the cluster may occur through simple bond fragmentation of the cation and/or by evaporation of monomers from the cluster.

In addition to these processes, there is also the possibility of the cation chemically reacting with one (or more!) of the solvating neutrals within the cluster (i.e., reaction 2). This intracluster chemical reaction then in turn generates a new product cluster ion. One may therefore visualize the electron-impact ionizer of the mass spectrometer as a *reaction cell* in which the precursor parent cluster ion (*the reagent*) is generated and allowed to *incubate* for microseconds. After this time period, any newly generated *product* cluster ions are interrogated by mass spectrometry in order to determine their chemical identities from their new masses. By observing this distribution of product cluster ions in the mass spectra, we can infer the ion–molecule chemistry that has occurred within the parent cluster ion. This analysis, however can be complicated by the fact that the newly generated product ion may undergo *additional* sequential reactions with other solvating molecules, within the same cluster.

A limitation of this technique is that one is unable to create a beam of neutral clusters of one specific size, but instead generates a broad distribution of cluster sizes. Hence, as is characteristic of mass spectrometric studies, one is unable to unambiguously define the relationship between the daughter product ion and the parent neutral cluster. However, as we will see later in this Account, this broad distribution of cluster size can be shifted by changes in the expansion conditions of the cluster beam.[30–32]

In addition to the extensive protonation chemistry (reaction 2) which has already been studied within clusters, our group has recently observed the generation of new cluster product ions that appear unique to the cluster environment. The observation of these new chemical processes[33] within a cluster is particularly exciting for chemists because we may be able to utilize the cluster as an exotic reaction medium, that is, a novel means by which to generate product ions that could not be produced by bimolecular gas-phase processes. We will give a demonstration of this new type of chemistry in the four following examples, which are selected from our own work.

Results and Discussion

1. Ammonia Clusters.[28] The ammonia cluster mass spectrum has been widely studied[14,15] and is dominated by a sequence of peaks with the empirical formulas[27] $\{NH_3\}_n^+$ and $\{NH_3\}_m NH_4^+$, corresponding to the previously discussed exoergic intracluster protonation reaction.

$$NH_3 + NH_3^+ \rightarrow NH_4^+ + NH_2 \qquad (3)$$

Careful study of the mass spectrum also reveals another sequence of peaks, which have the empirical formula $\{NH_3\}_{n-1}NH_2^+$. That is, they appear to result from the process of direct fragmentation of an N–H bond in the NH_3^+ cation, generating the NH_2^+ fragment intact within the cluster.

A plot of the ion intensities of the $\{NH_3\}_{n-1}NH_2^+$ ions as a function of cluster size (n), for a variety of experimental conditions, is shown in Figure 2. A magic number (an anomalous enhancement of the ion signal for a specific cluster size) is clearly observed for the cluster ion with size $n = 7$. This effect is insensitive to

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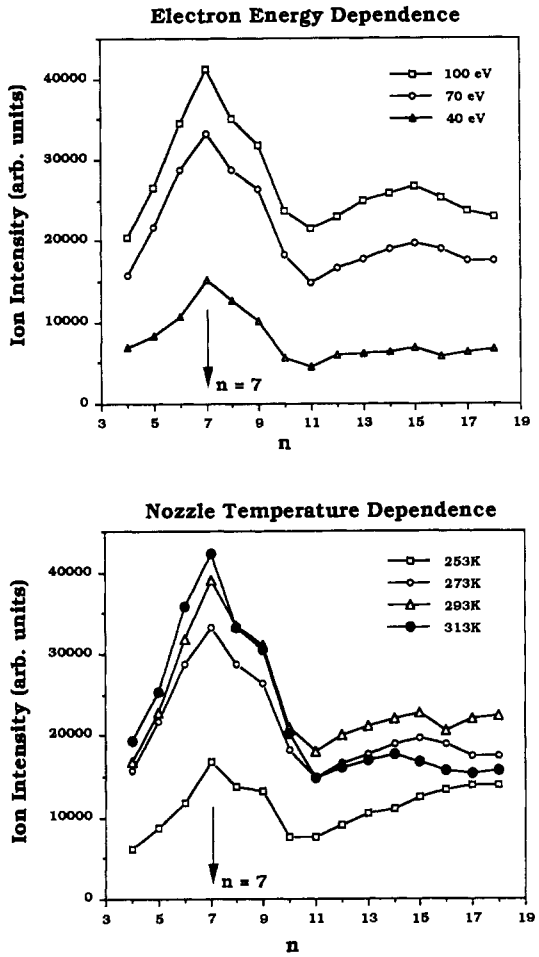

Figure 2. Intensity of $\{NH_3\}_{n-1}NH_2^+$ vs cluster size, as a function of electron-impact energy (T_0 = 273 K, P_0 = 1 atm) and as a function of stagnation temperature (70 eV, P_0 = 1 atm). Note the prominent magic number at n = 7. Reprinted with permission from ref 28. Copyright 1989 American Institute of Physics.

variations in the electron-impact energy (100–40 eV), the stagnation temperature (T_0 = 253–313 K), or the stagnation pressure (P_0 = 1–5 atm, not shown), indicating that this magic number is due primarily to the relatively large stability of the $\{NH_3\}_6NH_2^+$ cluster ion.[14,15]

This is a very surprising result in that magic numbers, for polar molecular systems, typically arise from the closing of the first solvent shell around the central cation. This is particularly true if the solvent molecules can directly hydrogen bond to the central cation. For example, in the case of the protonated ammonia cluster ion, n = 5 is observed to be especially stable (i.e., $\{NH_3\}_4NH_4^+$). The unique stability of this special cluster ion arises from the hydrogen bonding of four NH_3 molecules directly to the central NH_4^+ cation.[14,15] We may now ask the question, if the central cation in our case is indeed NH_2^+, why does the first solvent shell closure need six NH_3 molecules? Why wouldn't two or even three ammonia molecules suffice?

We can account for the observed size dependence of the $\{NH_3\}_{n-1}NH_2^+$ ion yield, by surmising that $N_2H_5^+$ has been formed within the cluster ion. In fact, if five NH_3 solvent molecules hydrogen bonded to the five H atoms of a protonated hydrazine, the cluster ion would have a completed solvation shell with the empirical formula $\{NH_3\}_6NH_2^+$. The cluster ion $\{NH_3\}_5N_2H_5^+$ has a total of seven nitrogen atoms and would account for

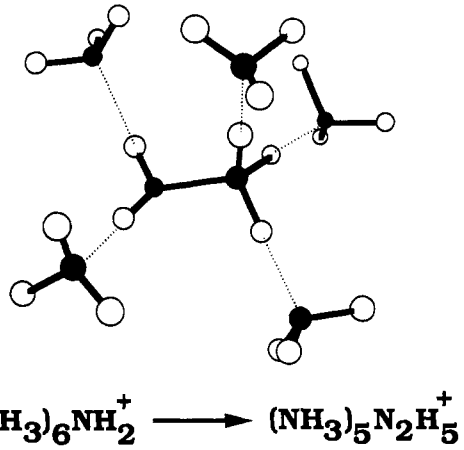

Figure 3. Proposed structure for $\{NH_3\}_6NH_2^+$ cluster ion. This species is the most prevalent of all cluster ions in the series $\{NH_3\}_{n-1}NH_2^+$ and is believed to be a protonated hydrazine molecule surrounded by one complete solvation shell of neutral ammonia's hydrogen bonded to the central cation. Reprinted with permission from ref 28. Copyright 1989 American Institute of Physics.

our observation of a magic number, n = 7. One likely structure for $\{NH_3\}_5N_2H_5^+$ is illustrated in Figure 3.

There are two possible candidates for the production of $N_2H_5^+$ within the ammonia cluster ion. The first is an associative, highly exoergic ($\Delta H°$ = −4.52 eV[34]), ion–molecule reaction between a nascent NH_2^+ ion and an adjacent NH_3:

$$NH_2^+ + NH_3 \rightarrow N_2H_5^+ \quad (4)$$

The second candidate is an endoergic ($\Delta H°$ = 1.12 eV[34]) ion–molecule reaction between the parent NH_3^+ ion and an adjacent NH_3:

$$NH_3^+ + NH_3 \rightarrow N_2H_5^+ + H \quad (5)$$

Of these two possible processes (reactions 4 and 5), we expect that reaction 4 will be the dominant producer of the $N_2H_5^+$ cation. This is due to the fact that, in the gas phase, reaction 5 is slow, occurring at a rate that is about 0.1% of gas-kinetic.[35] We also expect for various reasons[28,36] that the activation energy for reaction 4 is small if not negligible.

While the naked (unclustered) product of this highly exoergic associative reaction (reaction 4) would have sufficient internal energy to undergo additional N–H bond cleavage, the excited $N_2H_5^+$ product cation can be stabilized within the cluster by monomer evaporation. It is expected that the large exothermicity of reaction 4 should enhance this magic number effect, since the excess energy will serve to "boil off" the loosely bound solvent molecules which are not in the first solvent shell. This is an interesting example wherein the observation of magic numbers was necessary to elucidate the true chemical identity of the central cation.

As shown in Figure 4, reducing the diameter of the nozzle from 250 μm to 50 μm or changing the composition of the expansion mixture (neat NH_3 vs 3% NH_3

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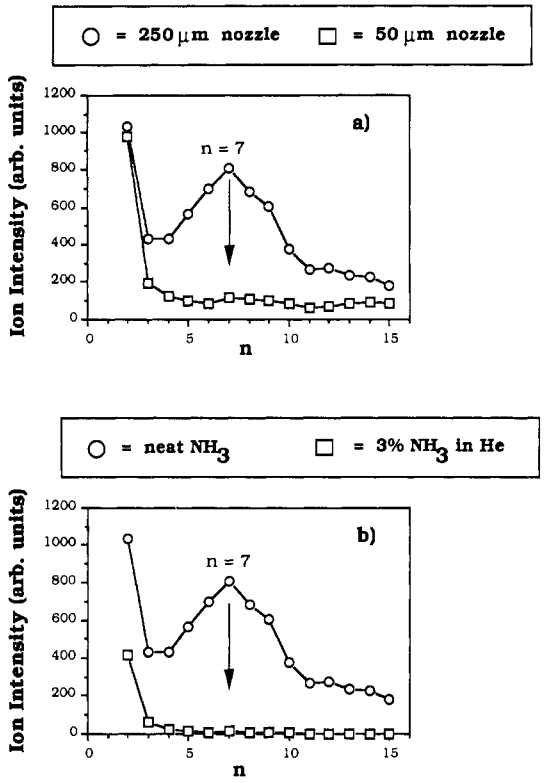

Figure 4. Ion intensity of $\{NH_3\}_{n-1}NH_2^+$ vs cluster size as a function of expansion conditions using 70-eV electron impact: (a) nozzle size (using neat ammonia); (b) expansion seeding (nozzle diameter = 250 μm). Note the loss of the magic number at n = 7 occurring for expansion conditions which generate smaller clusters.

in He) causes the magic number of $n = 7$ to disappear.[37] This change in ion intensity as a function of expansion conditions is also true for the magic number, $n = 5$, observed for the $\{NH_3\}_4NH_4^+$ species. This effect originates from the fact that the clustering process is less efficient when small expansion orifices or dilute seeded expansions are utilized.[30-32] Under such conditions, the broad distribution of neutral cluster sizes will be concentrated more toward smaller n. This suggests that the $\{NH_3\}_5N_2H_5^+$ and $\{NH_3\}_4NH_4^+$ cluster ions were both originally generated from extremely large neutral clusters. Following electron-impact ionization, the cluster ion must have undergone evaporation of many monomers, until it finally achieved the stable structure consisting of a closed solvent shell of ammonia molecules hydrogen bonded to a central cation.

Inspired by this result, Buck, Krohne, and Linnartz[38] have performed new experiments which involve size selecting (via a crossed molecular beam expansion) their neutral ammonia cluster beam prior to performing the mass spectrometry. Their work indicates that neutral clusters of $n > 25$ are necessary in order to observe the magic number for the $\{NH_3\}_4NH_4^+$ cation. This recent result demonstrates the tremendous amount of monomer evaporation that can occur within the cluster following the initial ionization/reaction event.

2. Ethylene Clusters.[39] The ethylene cluster mass spectrum is quite simple. In addition to the expected fragment peaks, it is composed of a sequence of cluster ions with the formula $\{C_2H_4\}_n^+$, which one could naturally attribute to the unreacted parent cluster ion (i.e., no protonation reaction). Figure 5 shows the intensity distribution of these "parent" cluster ions, $\{C_2H_4\}_n^+$, as a function of nozzle temperature. We observe that at decreased nozzle temperature or increased stagnation pressure (1.5–3.5 atm, not shown)[36] a very pronounced magic number appears with the empirical formula $\{C_2H_4\}_4^+$.

The observation that $n = 4$ is a magic number only under certain expansion conditions is difficult to explain solely in terms of stabilities of either the neutral or ionic parent ethylene clusters. In the previous discussion of ammonia clusters, a closed solvent shell hydrogen bonded to a central cation was the driving force for the appearance of a magic number. In a system, such as ethylene, where hydrogen bonding does not play a significant role, the observation of pronounced magic numbers is certainly not expected, since the distribution of neutral clusters is produced by processes that are essentially statistical in nature (i.e., why should the $\{C_2H_4\}_3C_2H_4^+$ cluster ion be so stable?). There would seem to be no a priori reason to predict that any particular ethylene cluster size should be extraordinarily stable. Since magic numbers are observed in such a system, it seems logical that the thermodynamic stabilities of the daughter ion cluster or neutral cluster parent are not the controlling factors.

High-pressure mass spectrometry by Kebarle and co-workers[40] has shown that the ethylene cation does undergo ion–molecule chemistry, that is, an exoergic[41] condensation reaction with a neutral C_2H_4 molecule.

$$C_2H_4 + C_2H_4^+ \rightarrow [C_4H_8^+]^* \quad (6)$$

The excited $[C_4H_8^+]^*$ is subsequently stabilized by collisions with the bath gas. This new $C_4H_8^+$ molecular cation can then also undergo successive condensation reactions with additional C_2H_4 molecules to form a larger and larger cation with the general empirical formula $C_mH_{2m}^+$. The rate of each successive condensation reaction decreases rapidly, and this decrease has been attributed to steric effects (i.e., the more highly branched $C_mH_{2m}^+$ product cations being less reactive).[40]

We now speculate that the observed ethylene cluster ions represent the products of a similar series of intracluster condensation reactions. The observation of the magic number at $n = 4$ (under expansion conditions which create extensive clustering) is then due to the formation of the $C_8H_{16}^+$ molecular ion generated via a series of successive ion–molecule reactions within the cluster. Since these condensation reactions are exothermic,[41] it is reasonable to expect extensive evaporation of unreacted monomers (as observed with the ammonia system). Neutral $\{C_2H_4\}_n$ clusters, with $n > 4$, following ionization via electron impact, can react within the cluster to give primarily the $C_8H_{16}^+$ cation, as shown in reaction 7. The intensity of these ions is

$$\{C_2H_4\}_{n-1}C_2H_4^+ \rightarrow \{C_2H_4\}_{n-2}[C_4H_8^+]^* \rightarrow \{C_2H_4\}_{n-3}[C_6H_{12}^+]^* \rightarrow \{C_2H_4\}_{n-4}[C_8H_{16}^+]^* \rightarrow n-4\,C_2H_4 + C_8H_{16}^+ \quad (7)$$

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(41) For the reaction $C_2H_4^+ + C_2H_4 \rightarrow C_4H_8^+$, $\Delta H° = -1.43$ to -2.60 eV, depending on the structure of the product.

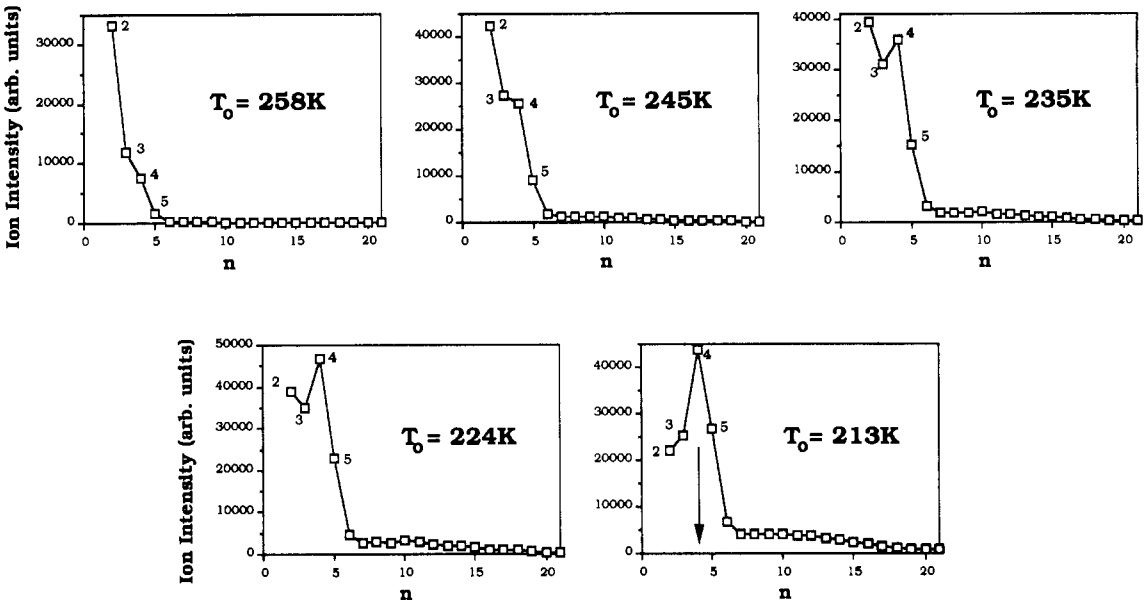

Figure 5. $\{C_2H_4\}_n^+$ ion intensity as a function of nozzle temperature: P_0 = 1.5 atm, nozzle diameter = 250 μm, and electron energy = 70 eV. Reprinted with permission from ref 39. Copyright 1990 Elsevier (Amsterdam).

expected to increase as the size distribution of the neutral ethene clusters grows larger (i.e., as either T_0 decreases or P_0 increases, n increases). The prominent peak at n = 4 represents a balance between the decrease in rate constant for each sucessive addition reaction and the evaporative loss of the remaining monomers.

We therefore attribute the origin of this magic number not to the stability of a solvated central cation but rather to the generation of a new molecular ion. We are now looking at other olefinic systems (propylene, butene, isobutene, CH_2CF_2) and have observed similar distinct magic numbers. As a result, this type of *intracluster ionic polymerization chemistry* appears to be a general class of reactions for this homologous series of unsaturated molecules.

3. Dimethyl Ether Clusters.[42,43] The bottom of Figure 6 shows a typical 70-eV electron-impact mass spectrum for $\{CH_3OCH_3\}_n$ clusters extending from the dimer to the trimer. In addition to the protonated cluster peaks resulting from the intracluster ion–molecule reaction

$$CH_3OCH_3 + CH_3OCH_3^+ \rightarrow (CH_3OCH_3)H^+ + CH_3OCH_2 \quad (8)$$

there are additional peaks corresponding to production of a hydronium ion (which has been reported before[42]) and protonated methanol ions,[43] each solvated by two dimethyl ether (DME) molecules. This sequence of cluster peaks is observed throughout the entire cluster mass spectrum to the limit of our sensitivity (n = 28).

It is interesting to note that while the CH_3^+ and $CH_3OCH_2^+$ fragment cations are extremely intense in the monomer mass spectrum of DME (~54% of all ion intensity), the corresponding *cluster* cations ($\{DME\}_nCH_3^+$ and $\{DME\}_nCH_3OCH_2^+$) are substantially reduced in intensity. We speculate that this is due to the fragments being consumed by an ion–molecule reaction within the cluster. One likely candidate is the ion–molecule reaction of the fragment cations with a neutral DME, within the bulk cluster, to form a trimethyloxonium cation intermediate, as shown in Figure 6 for the case of a tetramer. This type of ion–molecule reaction has been previously observed by Harrison and Young through the use of a tandem mass spectrometer.[44] This newly formed trimethyloxonium cation may then undergo different rearrangements to form the observed products as shown in Figure 6.

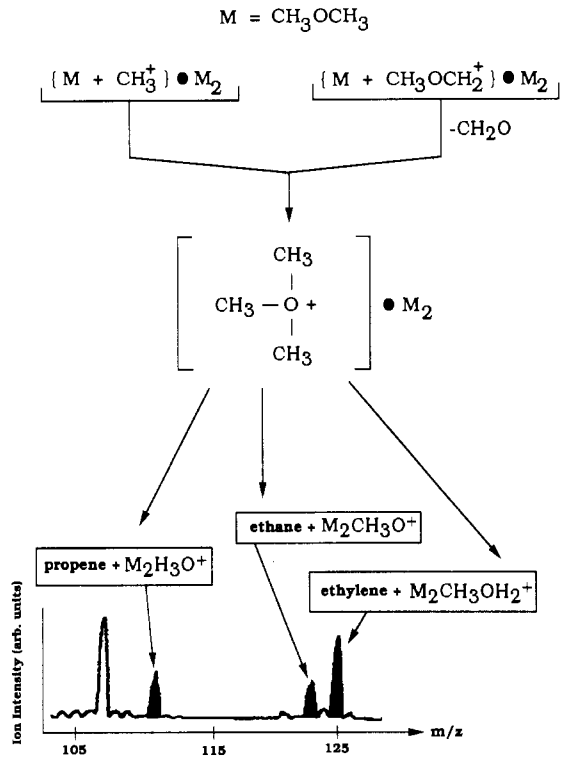

Figure 6. Proposed reaction mechanism for observed cluster ions generated through a common trimethyloxonium intermediate. Mass spectrum at bottom is for neat dimethyl ether cluster at 70 eV from dimer to trimer (80–140 amu). Major ion peaks are identified by their empirical formulas (M = $(CH_3)_2O$).

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This proposed mechanism is similar to that invoked for the decomposition of DME over zeolite catalysts. van Hooff et al.[45] observed that conversion of DME over a zeolite catalyst produced ethylene and propene as primary olefins. To account for their results, they speculated that a trimethyloxonium intermediate was responsible for all of the observed products. We also suggest that the DME cluster reactions leading to the same products involve a similar mechanism found to occur on zeolite catalysts. Within the stabilizing environs of a cluster, the trimethyloxonium cation may now internally rearrange, where it then forms protonated methanol (via elimination of ethylene) or protonated water (via elimination of propene).

4. 1,1-Difluorethane Clusters.[46] As described in the Introduction, the dominant reactive process that occurs within the majority of cluster ions is the generation of a protonated ion via a bimolecular reaction between the monomer cation and one of the neutral solvent molecules (reaction 2). However, for many organic molecules, upon electron-impact ionization, the parent ion is not observed via mass spectrometry. This is due to the ground-state parent cation (M^+) being thermodynamically unstable with respect to various fragmentation channels. In such cases the mass spectrum is composed solely of fragment ions, and identification of the molecule must be made by the characteristic fragmentation pattern.

The mass spectrum of 1,1-difluoroethane (DFE) represents just such a case. Since the parent ion is unstable, it should not survive long enough to react with any of the solvating monomers. Hence, the cluster mass spectrum of DFE should be composed solely of solvated fragment ions,[49] generated primarily by loss of F, as shown in reaction 9. The protonation reaction (reaction 10) should be unimportant, and there should be a complete absence of protonated cluster peaks ($M_{n-1}H^+$).

$$\{CH_3CHF_2\}_n^+ \rightarrow \{CH_3CHF_2\}_{n-1}CH_3CHF^+ + F \quad (9)$$

$$\{CH_3CHF_2\}_n^+ \rightarrow \{CH_3CHF_2\}_{n-1}H^+ + CH_3CF_2 \quad (10)$$

Figure 7 shows a bar graph of percent yield as a function of cluster size for both loss of F (generation of $M_{n-1}CH_3CHF^+$) and the protonation reaction (generation of $M_{n-1}H^+$). Surprisingly we see that the sequence of peaks that have the empirical formula of $M_{n-1}H^+$ *does* appear at $n > 4$ and continues to become progressively more prominent with increasing cluster size. This is in direct contrast to the loss of F channels which monotonically decrease with increasing cluster size (as do all the other fragment channels for this molecule.)[47]

As Jungen and co-workers point out,[48] a parent ion might be observed as a metastable ion if it is formed in the Franck-Condon region of the neutral molecule. Thus, if the parent ion is generated within a van der Waals cluster, the presence of solvating molecules may stabilize it long enough, such that it can react with one of the neutral monomers via reaction 10. The fact that the production of protonated cluster ions has a prominent onset for $n > 4$ suggests that a "critical" neutral cluster size is necessary for stabilizing the parent ion. This case demonstrates the utility of studying chemistry within ion clusters, in that unstable reagents (such as the $CH_3CHF_2^+$ cation) can be stabilized within the solvating environment long enough to react with a neutral monomer, a reaction that could not occur in the gas phase.

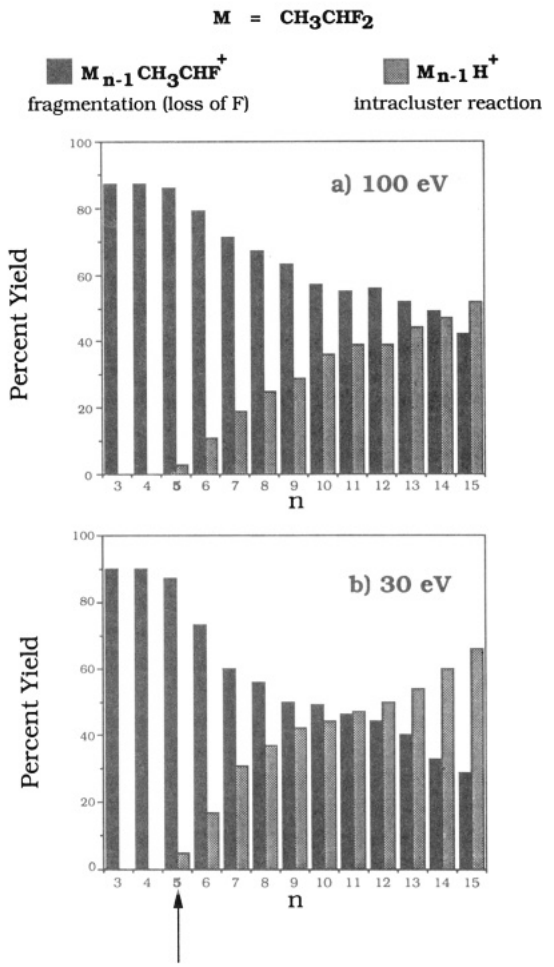

Figure 7. Bar graph representing percent yield of daughter cluster ion as a function of cluster ion size (n) at 100- and 30-eV electron-impact energies. Note how the fragmentation channel (loss of F from the cation) decreases as a function of n while the protonation reaction has a sudden onset at $n = 5$ and increases as a function of n.

Future Directions

These examples represent a sampling of the new cluster chemistry that we have recently observed. It should be noted that this extensive chemistry is not limited to singly charged clusters but can also occur within multiply charged cluster ions, as well.[49] Likewise one is not confined to ion–molecule chemistry but can also involve neutral chemistry within the cluster, via the use of various photodissociation techniques.[50] In point

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of fact, this is truly only the beginning in terms of the new chemistry that can be discovered within van der Waals clusters.

Thus, while the study of reactive processes in clusters may be utilized as a conceptual bridge between the "bimolecular" gas-phase collisions and the "solvated multimolecular" world of chemical reactions in solution, we sense that this bridge has in fact turned into a crossroads. Novel chemical reactions and unexpected dynamics can be observed that occur within the stabilizing environment of a molecular cluster by (1) providing novel chemical pathways (as in the cases of $\{NH_3\}_n^+$, $\{C_2H_4\}_n^+$, and $\{CH_3OCH_3\}_n^+$) and (2) stabilizing unstable reagents (as in $\{CH_3CHF_2\}_n^+$). New experimental directions we hope to employ within the near future are two-fold. The first involves exploring negative ion chemistry within clusters via techniques similar to those described in this paper. The second is the use of laser-induced fluorescence, to probe the internal states of the neutral radical product generated via these exoergic ion–molecule cluster reactions (NH_2 produced via reaction 3, for example).

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Molecular Dynamics Simulations with Experimental Restraints

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Molecular dynamics simulations of biological macromolecules have many applications.[1] In addition to providing dynamical information (e.g., the magnitude and time scale of fluctuations; the relaxation after a perturbation such as ligand photodissociation), they can serve as a tool for exploring the conformational space of the molecule. One can distinguish between two different cases where this feature of molecular dynamics simulations is used. One of these requires the generation of Boltzmann-weighted ensembles to compute equilibrium thermodynamic properties and free energy changes in the system.[2] The other depends only on the generation of a representative sample of conformational space without the need for proper Boltzmann weighting. This has been used in studies of protein folding[3] and, more recently, has been applied to three-dimensional structure determination and refinement of macromolecules based on experimental information. It is the latter that is the focus of this Account.

Molecular dynamics simulations of macromolecules have a demonstrated utility in providing an atomic model that is in accord with the experimental information. A case in point is the determination and refinement of three-dimensional structures of proteins and nucleic acids in solution by nuclear magnetic resonance (NMR) spectroscopy.[4] Another example is the refinement of three-dimensional structures of macromolecules based on crystallographic diffraction data.[5] The experimental information is incorporated into the simulation by using a hybrid energy function,[6]

$$E^{\text{pot}} = E_{\text{chemical}} + wE_{\text{experimental}} \quad (1)$$

where E_{chemical} is an empirical energy function that provides information about equilibrium covalent bonding geometry, vibrations, hydrogen-bonded interactions, and nonbonded interactions,[7] and $E_{\text{experimental}}$ consists of an expression for the difference between observed and computed data which is equal to zero if the model matches the data perfectly; the form used for

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