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CRITICAL INSIGHT

Are Clusters Important in Understanding the Mechanisms in Atmospheric Pressure Ionization? Part 1: Reagent Ion Generation and Chemical Control of Ion Populations

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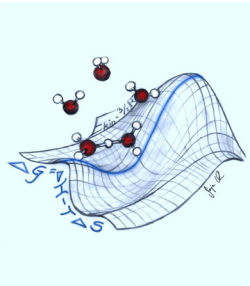

Abstract. It is well documented since the early days of the development of atmospheric pressure ionization methods, which operate in the gas phase, that cluster ions are ubiquitous. This holds true for atmospheric pressure chemical ionization, as well as for more recent techniques, such as atmospheric pressure photoionization, direct analysis in real time, and many more. In fact, it is well established that cluster ions are the primary carriers of the net charge generated. Nevertheless, cluster ion chemistry has only been sporadically included in the numerous proposed ionization mechanisms leading to charged target analytes, which are often protonated molecules. This paper series, consisting of two parts, attempts to highlight the role of cluster ion chemistry with regard to the generation of analyte ions. In addition, the impact of the changing reaction matrix and the non-thermal collisions of ions en route from the atmospheric pressure ion source to the high vacuum analyzer region are discussed. This work addresses such issues as extent of protonation versus deuteration, the extent of analyte fragmentation, as well as highly variable ionization efficiencies, among others. In Part 1, the nature of the reagent ion generation is examined, as well as the extent of thermodynamic versus kinetic control of the resulting ion population entering the analyzer region.

Keywords: Atmospheric pressure ionization, Ion bound clusters, Cluster equilibria, Ion–molecule reactions, Ion activation, CID

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Introduction

Much has already been written about the importance of clusters in atmospheric pressure ionization (API) sources of mass spectrometers. There is a clear consensus that they are important and universally present. In terms of published work related to mass spectrometer ion sources, these have been reported in atmospheric pressure chemical ionization (APCI) [1, 2], atmospheric pressure photo ionization (APPI) [3, 4], dopant assisted (DA)-APPI [5–7], dopant assisted atmospheric pressure laser ionization (DA-APLI) [8, 9], dielectric barrier discharge ionization (DBDI) for ambient ionization [10], flowing atmospheric pressure afterglows (FAPA) [11], direct analysis in real time (DART) [12, 13], desorption APPI [14] (DAPPI), etc., this list can be continued to a number of well above 50 entries [15]. Clearly many of these techniques differ by their individual primary ion generation mechanisms, initiated by either kinetically

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hot electrons and/or photons of sufficient energy, and yet they all seem to somehow generate protonated molecules $[M + H]^+$, at least to a quantifiable extent. It has been repeatedly speculated and/or concluded that clusters are involved in the overall ionization mechanisms. As one example, in a recent review of the mechanisms operative in ambient ionization sources, Chen et al. summarized the relevant cluster chemistry initiated by helium metastables (He^M) and resulting in proton bound water clusters by the following mechanism:

$$He^M + n\,H_2O \rightarrow \left[H + H_2O_{(n-1)}\right]^+ + He + OH^- \quad \text{(Reaction1)}$$

The authors further concluded [16]: "These clusters are the reactants for proton transfer ionization via Kebarle's water displacement reaction

$$\left[H + (H_2O)_n\right]^+ + M \rightarrow \left[H + H_2O_{(n-1)} + M\right]^+ + H_2O \quad \text{(Reaction2)}$$

It should be obvious that clusters are important if one considers that a typical ion–molecule dipole binding energy is on the order of 1 eV versus an ambient thermal room temperature collision energy of about 0.02 eV. Citing Kebarle again, the binding energy of H_3O^+ with H_2O is about 1.37 eV and a strong binding energy for H_2O with $[H + (H_2O)_n]^+$ remains even for larger clusters (e.g., 0.5 eV for $n = 4$) [17]. Given the known propensity for forming ionic clusters under ambient atmospheric conditions, it is valid to question why this article is required at all. Below are a few justifications:

- First, there are some remaining "mysteries." Citing the case for helium metastables (He^M), it is a fairly complicated mechanism leading to the frequently observed $[M + H]^+$ signal in the mass spectrum—even if cluster chemistry is taken into account. Reaction 1 represents a long cascade of bi- and termolecular reactions, many of which involve forming highly dynamic yet closely coupled equilibria. If the analyte M is successfully competing with water in proton bound clusters (Reaction 2 is in fact an equilibrium *system*), then clearly other matrix molecules could be engaged as well. For example, it is common to use polar solvents when API is coupled to liquid chromatography and these species could be engaged in reactions analogous to those described by Reaction 2 and, therefore, there could be competitive concentration-driven equilibria, even though the extent of these is hard to predict. As a matter of fact, numerous ion–molecule reaction rate constants are of comparable magnitude; thus, the most abundant neutral species other than nitrogen may participate in many such equilibria. Further, the observation that per-deuterated dopants used in DA-APPI generate mainly protonated molecules [18] is initially not very helpful for a deeper mechanistic understanding.[1] The same holds true for the observation that the non-protic APPI dopant carbon disulfide also generates mainly protonated analyte ions [19]. It appears as if cluster chemistry again plays the central role in rationalizing this phenomenon. These are only two examples demonstrating the complexity of the chemistry involved between the primary ionization event and the recording of the mass spectrum. Clearly, a comprehensive article explaining these observations is needed.
- Second, clusters seem to be ubiquitous in *thermalized* API chemistry. A closer inspection reveals that they are frequently of the type $[H + (S)_n]^+$ (i.e., proton bound "solvent" (S) clusters), with S being a proxy for polar molecules. Furthermore, in the case of $S = H_2O$, the cluster population (n) appears to be thermally equilibrated with $n = 4 \ldots 8$ being most abundant [20]. How do these cluster species tie into the overall ionization mechanism? It is certainly not via their gas phase acidity; clusters of this size are virtually chemically "non-reactive" with respect to bimolecular protonation reactions. Such issues need to be resolved. Owing to limitations to the length of this paper, we center the remaining part of the cluster chemistry discussion on water. It is strongly pointed out that typical LC solvents such as methanol or acetonitrile, when present at elevated mixing ratios, will actively participate in cluster chemistry as well.
- Third, the fact that clusters are not commonly observed in modern API mass spectrometers, at least when browsing through the literature of the past two decades, is readily explained; however, it is worth reiterating *why* this is the case. Naturally, mass spectrometrists tend to believe in what they are seeing—and in this case what they are observing are mass spectra. No observable clusters in the spectra may then lead to the presumption that clusters do not participate in the ionization mechanism at all, because they are not "there." In addition, with respect to many analytical tasks it may not even be worth heeding the impact of cluster chemistry at all—if a molecule M is detectable as $[M + H]^+$, then why bother?
- Fourth, a good alternative answer to the title question "*Are* clusters important in API mass spectrometry" could also be "42"[2] instead of "Yes they are" already given

[1] At first sight this appears to be the ultimate success of alchemy: deuteron/proton transmutation.

[2] This is the answer Deep Thought, a mighty super-computer replied (after 7.5 million years of computation time) to the question about "Life, the universe, and everything" [21]. And for sure generations of students have pulled that answer to get at least partial credit for working through tough PChem exam questions. And many instructors have done exactly that: award partial credit. But only if the student did in fact *not know what the question really was*: "I'm afraid that the Question and the Answer are mutually exclusive. Knowledge of one logically precludes knowledge of the other. It is impossible that both can ever be known about the same universe. Except if it happened, it seems that the Question and the Answer would just cancel each other out and take the Universe with them, which would then be replaced by something even more bizarrely inexplicable. It is possible that this has already happened" [22].

above. A question that asks for a more constructive answer appears to be "*When* do clusters become important in API mass spectrometry?" This phrasing allows us to define boundary conditions before we come up with more definite answers than 42.

To clarify things upfront: a couple of manuscript pages simply cannot cover it all. We are thus narrowing the discussion to API methods which potentially build clusters bottom up: Individual primary ions are generated, these induce bi-/termolecular reactions eventually leading to thermalized ionic products, which then establish a complex system of closely coupled highly dynamic equilibria, in turn resulting in the stationary concentrations of the ionic species present in the API source. This is in contrast to the (still) rather elusive ion generation processes in ESI and its derivatives, where ions are expelled or evaporating from micro droplets, or are generated in rather complex Coulomb explosions. These latter, in the widest sense top down processes, are thus not subjects of this article. In other words, we are fully aware that this restriction is significantly narrowing the discussion; however, the liquid–gas phase transition including aerosol formation and ion dynamics is a sufficiently complex process that calls for an article of its own.

Let us again take a DART source operated with helium as an illustrative example of the complexity of apparently pure gas phase API mechanisms, excluding all heterogeneous or phase transfer reactions. The original aim of DART (or what one expects at first sight considering its experimental setup) is Penning ionization of a sample, yielding molecular ions [23]

$$He^M + M \rightarrow M^{\bullet+} + e^- + He \qquad \text{(Reaction3)}$$

followed by the complex (and somewhat surprising) transformation of the radical cation into a protonated molecule, since in practice the majority of samples yield $[M + H]^+$ ions [16, 24]. These experimental findings are worth exploring a little further.

In essence, the DART method generates primary charge carriers in a corona-to-glow-discharge-transition plasma [11]. Such discharges belong to the group of low temperature plasmas (LTPs), together with coronas used in APCI, FAPA, APGDs, DBDs, and many more discharge types. Characteristic of all LTPs is their non-equilibrium and chemically active behavior. LTP modes of operation are strongly affected by the presence of neutral species [25]. In non-equilibrium LTPs, electrons are generally "hot" (up to 25 eV), whereas ions and neutrals are close to "thermalized" (0.02 to 0.1 eV). It is also worth noting that such electrical discharges generate significant amounts of vacuum ultra violet (VUV) radiation, which potentially leads to ionization processes as well. Each He^M atom abundantly generated via discharge chemistry in DART carries about 20 eV of electronic energy[3] and may, thus, ionize a broad variety of molecules with favorable cross sections. However, ionization of the analyte M is not the only thing that may happen: the He^M generated will travel mostly with thermal velocities around 500 m/s. On the microscopic scale, it is very likely that *if* He^M encounters an analyte molecule, a process analogous to the Alderaan catastrophe[4] happens to the target molecule as well. He^M-Penning ionization at low pressure ($5 \cdot 10^{-4}$ mbar) leads to fragment ions that are even more abundant than observed in 70 eV electron ionization (EI), as demonstrated for anisole [28] (70 eV abundances given in parentheses).

$$He^M + C_6H_5OCH_3 \rightarrow [C_6H_5OCH_3^{\bullet+}]^* + He + e^- \quad 0.46(0.95) \qquad \text{(Reaction4)}$$

$$[C_6H_5OCH_3^{\bullet+}]^* \rightarrow [M-15]^+ + CH_3^{\bullet} \quad 0.08(0.17) \qquad \text{(Reaction5)}$$

$$\rightarrow [M-30]^{\bullet+} + CH_2O \quad 0.44\ (0.93) \qquad \text{(Reaction6)}$$

$$\rightarrow [M-31]^+ + CH_3O^{\bullet} \quad 0.49\ (0.27) \qquad \text{(Reaction7)}$$

$$\rightarrow [M-43]^+ + CH_3^{\bullet} + CO \quad 1.00(1.00) \qquad \text{(Reaction8)}$$

$$\rightarrow [M-57]^+ + CH_3O^{\bullet} + C_2H_2 \quad 0.26\ (0.25) \qquad \text{(Reaction9)}$$

$$\rightarrow [M-69]^+ + CH_3^{\bullet} + CO + C_2H_2 \quad 0.96\ (0.58) \qquad \text{(Reaction10)}$$

Energy transfer to a molecular ion appears to be substantial in He^M-Penning ionization [29]. It becomes apparent that analyte molecules in direct contact with a non-equilibrated LTP chemistry are exposed to a very harsh chemical environment, comparable to 70 eV EI. The term

[3] He^M represents the lowest electronically excited 2^3S_1 state of He and lies 19.82 eV above the 1^1S_0 ground state, which is the greatest amount of energy that can be stored in any atomic or molecular system. The $2^3S_1 \leftarrow 1^1S_0$ transition is dipole and spin forbidden but can well occur upon collision of ground state He with fast electrons as they are present in LTPs. The lifetime of He 2^3S_1 is about 8000 s [26].

[4] In comparison to the extremely light and swiftly moving electron, He^M is more like a Death Star loaded with an enormous amount of energy ready to be released when slowly coming about; recall the fate of Alderaan [27]. In a very nice article on He^M Baldwin writes: "*They behave like nano-hand grenades …*" [26]

"low temperature" is thus misleading; 20 eV of electronic energy per He^M atom corresponds to a Boltzmann temperature largely exceeding 10,000 K [30]. This notion, however, is in bold contrast to the observed "softness" of the ionization process when using (e.g., DART). Upon formation in a "hot" zone, molecular ions carrying excess internal energy are expected to undergo extensive fragmentation. DART ionization of anisole at AP, however, produces little or no fragment ions [24]. Considering these observations, it may be worth having a brief look at the fundamental differences between vacuum ionization and API before we go on. Table 1 summarizes some experimental parameters along with crucial elementary processes operative in the *ion source* region. With Table 1 at hand, the alleged soft versus hard ionization contradiction discussed above is readily resolved. At atmospheric pressure, collisional deactivation can compete to a large extent with fragmentation (i.e., unimolecular decay reactions) up to rate constants of about 10^9 s^{-1}, which is a fairly large value [31, 32]. Thus, fragmentation at AP is only minimal, as observed. In detail: very high gas density and very high collision rates at atmospheric pressure give rise to reactions of metastable helium atoms He^M with other gas phase components such as N_2, O_2, H_2O, and solvent vapor. Newly formed reactant ions can then react with sample molecules. Excited molecular ions formed in Reaction 4 may undergo substantial deactivation by numerous collisions with neutrals. The implications for our example of DART ionization of anisole are as follows. Molecular ions formed by He^M Penning ionization may lose excess internal energy by collisions, so minimal fragmentation takes place, at least if the rate of fragmentation is slower than the collision rate. Alternatively, He^M may generate $N_2^{\bullet+}$ or $O_2^{\bullet+}$ ions,

$$He^M + N_2(O_2) \rightarrow N_2^{\bullet+}(O_2^{\bullet+}) + e^- + He \quad \text{(Reaction11)}$$

which ionize anisole by charge exchange and impart much less internal energy to the anisole molecular ion.

Table 1. Experimental Boundary Conditions and Elementary Processes Operative in Vacuum Ionization and API. "Yes" and "No" are Strongly Simplified and There are Obviously a Number of Exceptions

Parameter	API	Vacuum Ionization
Pressure	1000 mbar	10^{-6} mbar
Mean free molecular path	100 nm	100 m
Hard sphere collision number	10^9 s^{-1}	1 s^{-1}
Number densities O_2/H_2O	O_2: 10^{14} … 10^{18} molecule cm^{-3} H_2O: 10^{13} … 10^{16} molecule cm^{-3}	10^4 … 10^7 molecule cm^{-3}
Ion specific numbers	API	Vacuum Ionization
Source residence time	10 ms … 1 s	< 1 μs
Unimolecular decay	"No"	"Yes"
Bimolecular reactions	Yes	No
Termolecular reactions	Yes	No

$$N_2^{\bullet+}(O_2^{\bullet+}) + M \rightarrow M^{\bullet+} + N_2(O_2) \quad \text{(Reaction12)}$$

Looking at the ambient mixing ratios of nitrogen, oxygen, and water, it appears as if the most probable DART cascade is represented by

$$He^M \Rightarrow N_2^{\bullet+} \Rightarrow H_2O^{\bullet+} \Rightarrow \left[H + (H_2O)_n\right]^+ \quad \text{(Reaction13)}$$

and, thus, protonation of "polar" (higher proton affinity) samples may occur as well [11, 24] (cf. Reaction 2). Note that ground state $O_2^{\bullet+}$ does not react with water.

In conclusion, there is much more going on in API than what one expects from the neutral bulk gas composition. This will be further elaborated below for the formation of cluster ions.

Discussion

Chemical Domains in API MS

For a structured discussion, it is reasonable to first decouple the "hot" primary charge generating chemistry from the subsequent "thermalized" chemistry, where all molecules, radicals, and/or atoms have relaxed to the electronic ground state and travel with thermal Maxwell-Boltzmann type translational velocity distributions. A valid question is: What are the appropriate parameters to use in order to distinguish between these two domains? Additionally, can we define other distinct *chemical* domains within the overall API MS ion generation and detection process?

The good news is that there are more or less clearly definable chemical domains. Let us briefly step through the entire ion generation, transport, and detection process with the aim of identifying decoupled chemically active domains operative in API MS. The sketch in Figure 1 will be used to aid in the discussion.

Upon moving from left to right in Figure 1, the change of the properties of the chemical environment that ions encounter could not be more dramatic. There are at least seven distinct domains in which the characteristics of the "moving matrix" are significantly changing with respect to the chemical composition, pressure, and temperature, and, consequently, reaction kinetics and dynamics. Let us briefly consider each of these domains in the order of occurrence from energy input to ion detection. In the remaining part of this first paper, we focus entirely on the *thermal* ion source chemistry, i.e., on the chemistry prevailing in domain 2 – or – the ion source chemistry. The impact of traversing domains 3 to 7 on the ion population will be discussed in the second part of this paper series.

Domain 1: The "Hot" Primary Ion Generation Chemistry—Energy

This is the region where highly energetic species such as He^M, VUV, UV, and visible light are present. Light is generated either via emission form the "hot" LTP zone or from an external

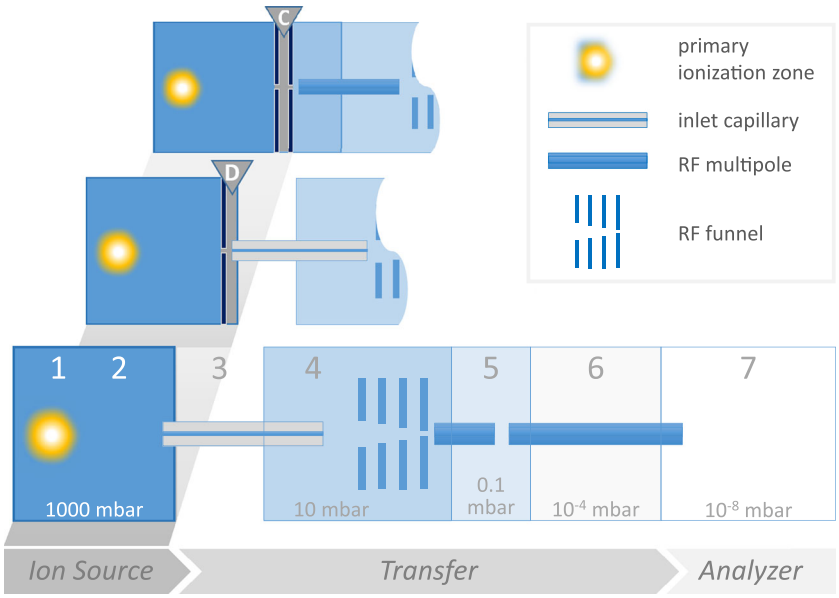

Figure 1. Sketch of typical API MS configurations [33, 34]. Numbers 1–7 refer to the domains discussed further below. The pressures given may vary considerably; RF funnels and RF multipoles are shown in arbitrary geometries and configurations. All ion optical elements may be considerably biased with DC voltages. Bottom: ion source coupled via a capillary to the vacuum system of the analyzer (e.g., Thermo-Fisher). Center: same as previous but additional directed "dry" (D) gas flow through a biased sampling electrode ("spray shield"; e.g., Bruker Daltonics, Agilent Technologies). Top: ion source coupled via orifices to the vacuum system of the analyzer; additionally a curtain (C) gas flow is directed into the source, and a differential pumping stage (e.g., AB SCIEX)

light source (APPI/APLI). It is worth noting that ion sources generating appreciable visible light emission, such as spark sources, glow discharges, and low temperature plasmas also generate appreciable VUV light that affects chemistry probably as much as the noble gas metastable species present. It appears to be reasonable to define this area in terms of emission intensity: "The light goes out" corresponds to "having crossed the border" of this domain.

Domain 2: The Thermalized API Chemistry—Tranquility

Next to domain 1 is the fully thermalized region of tranquility within the AP ion source. In fact, this is the chemically most relaxed environment in which ions reside on their passage to the detector. In this region, electrical fields cannot do much with respect to energizing the matrix (see below). Electrical fields as well as fluid dynamic forces may gently push the ions towards the analyzer orifice; in many modern API mass spectrometers, this is the upstream port of a capillary or the orifice of a differentially pumped nozzle or skimmer assembly.

Domain 3: The Flow into the Entry Port of the Mass Spectrometer—Turbulence

Once the ions have entered the sampling port, the swift acceleration of the bulk gas leads to a more or less violent turbulent flow. Additional gas flows, such as a "curtain gas" between two nozzles or a "dry gas" in front of the capillary (cf. Figure 1) strongly promote the overall turbulent nature of the gas motion within this domain. The older literature states that laminar conditions prevail in such capillaries [35, 36], but recent experimental results strongly suggest that only a fully developed turbulent flow leads to the determined flow properties and ion transfer times [37, 38]. It is reasonable to assume vigorous mixing of all matrix components. The impact of such flow conditions on the ion population remains unclear and is subject to several studies in our labs including the effect of elevated wall collision numbers with capillary ducts. This domain does not exist in all API instruments; for instruments without a capillary, using instead a thin-walled orifice as the restriction between AP and the downstream vacuum, domain 4 begins immediately after domain 2.

Domain 4: Expansion and Compression—Cluster Growth and Re-Equilibration

The fourth domain is initially dominated by the dynamics of the gas expansion from the capillary or nozzle/skimmer exit into the sustained background pressure of a few mbar in the first pumping stage. At the origin of the expansion, a local pressure of a couple of hundred mbar prevails as consequence of choked flow [39]. Such conditions lead readily to significant adiabatic cooling and thus a completely new

chemistry frequently observed in supersonic jet expansions. For example, there may be fast growth of cluster structures through condensation processes, particularly when charges are present and the partial pressure of polar matrix components is high [40]. At the same time, the mean free molecular path of the matrix components increases strongly from less than a micron in the source and capillary region to millimeters within this domain.

Domain 5: Ion Guiding—Ion Activation

Depending on the analyzer geometry, electrically biased skimmers and/or ion funnels are used for ion guiding purposes. Ions are supposed to enter the next pumping stage, while neutrals are supposed to be pumped away. The guiding process is rather interesting: with a mean free path in the millimeter range, and being accelerated by electric fields in the region, ions can gain significant kinetic energies between collisions and they can be easily pushed in a certain direction. In introductory Physical Chemistry courses, it is well established that molecular kinetic energy can be translated into a translational temperature [41]. Using such calculations, it is surprising how high these temperatures may become in this domain, and in practice—depending primarily on the bias voltages between the adjacent ion optical elements and the RF voltages applied on the ion guides—ion activation and the fragmentation can be substantial. This issue will be discussed in much more depth in Part 2 of this series.

Domain 6: Ion "Cooling"—Severe Ion Activation

Upon entering this domain, the local background pressure drops to roughly 10^{-3} mbar. Further funnel structures or multipoles are used to "cool" the ion beam with respect to minimizing velocity vector components orthogonal to the direction of forward travel as well as to narrow the velocity distribution in the forward direction [42]. The same factors discussed for domain 5 apply here as well, but are even more pronounced. The mean free path increases, as well as the energy acquired by the ionic species between collisions, depending again on the local electrical field. Note that the electrical field *within* the ion guide structures themselves is actually quite low in the forward direction, but the kinetic energy of the ions may still be high because of the bias voltage between the guides and also because of the applied rf voltage. Fragmentation becomes rather easy in this region and, hence, it is commonly used to collisionally dissociate parent ions in tandem MS instruments.

Domain 7: Space—The Final Frontier

After this more or less rough ride through the ion transport region, the background pressure finally drops to values leading to mean free molecular paths on the order of tens of meters, i.e., the essentially collision-free region. Since "Chemistry" is the result of nothing more than successful inelastic or reactive collisions, this region is essentially a chemistry-free zone (provided unimolecular decay of metastable molecular ions is not taking place …). This is of course only true for analyzer systems that do not require further collisional damping upon mass analysis, such as quadrupole ion traps. Time of flight analyzers, conventional quadrupole filters, ion cyclotron resonance cells, and the Orbitrap analyzer are usually regarded as "space"[5] … *but not* their upstream injection traps or ion guide/focusing multipoles where reactive collisions may well occur.

Taking Stock …

This paper is concerned with the impact of cluster ion chemistry on the measured ion signal distribution. Since clusters are rather fragile charged species, they have only two chances to survive the entire passage to the analyzer: (1) Embedded within a supersonic free jet, which is not desirable because of the mentioned adverse impact of adiabatic cooling on the local chemistry, see domain 4. (2) Within thermal equilibrium with the background matrix, which dictates rather shallow electrical field gradients, particularly in domains 4–6, typically resulting in significant ion losses during transport. In other words, either clusters are measured close to their thermal distribution (in many instrument designs at the expense of significantly lowered sensitivities) or the cluster population may be considerably shifted towards smaller size distributions—in the extreme to bare ions—albeit with high ion transmission factors and, thus, sensitivity.

When we further narrow the scope of the paper to the *impact of thermal cluster chemistry* on the *ionization mechanism*, we are focusing our attention entirely on domain 2, the API source. This appears to be a very good starting point—Part 1 of this paper series is thus devoted to general aspects of the chemistry prevailing in domain 2. We will expand the discussion in Part 2, by attempting to understand why clusters virtually fall into oblivion in modern API instruments.

Thermal Ion Chemistry in the API Source Region: General Considerations

The word "Chemistry" is analogous to the word "Change." That is "Change" of chemical identities and, thus, naturally change of the concentrations of reactants and products. These processes may be described as being driven by the gradient of the Gibbs function G of the reaction system [41]. The change in G when aspiring towards a minimum is a

[5] "Space … is big. Really big. You just won't believe how vastly, hugely, mind-bogglingly big it is. I mean, you may think it's a long way down the road to the chemist's, but that's just peanuts to space" [43].

function of the local temperature and pressure and of the sum of all chemical potentials of the k species present in the reaction system below in Equation (1),

$$dG = \left(\frac{\partial G}{\partial p}\right)_{T,n} dp + \left(\frac{\partial G}{\partial T}\right)_{p,n} dT + \sum_i^k \nu_i \left(\frac{\partial G}{\partial n_i}\right)_{T,p,n_j \neq n_i} d\xi \quad (1)$$

with n as molar amount, ν as stoichiometric coefficient, and ξ as the extent of reaction variable. Thermodynamics is inherently "timeless" though, in that everything is governed solely by energy changes. Thermodynamics does not care *when* a respective energy minimum is attained; it may be within micro seconds or within the lifetime of the universe. With respect to API chemistry, we can state that if a chemical system is reaching $dG = 0$ within the dwell time of ions in the source region, the ion concentration changes are *thermodynamically* controlled and we may apply thermodynamic properties for an assessment of the concentrations present. If that is not the case, i.e., the system does not get even close to $dG = 0$ within this time frame, then *kinetics* is controlling the concentrations present and we have to use individual rate constants to assess the temporal evolution of these concentrations. To understand whether thermodynamic or kinetic control exists in typical API sources, we first need to have a good look at the room conditions.

Typical API Conditions

Classical vacuum ion sources are generally "clean." The background pressure is 10^{-6} mbar or better. In the good-ol' days, ion sources were baked out on a regular basis. The partial pressure of water was far below 10^{-10} mbar. API sources are the exact opposite: Everything is "wet, wild, and dirty." Even when using ultra clean nitrogen gas from the boil-off of liquid nitrogen tanks[6] the mixing ratio of water in the ion source region will very rarely—if ever—go below 1 ppmV. This is because, first, none of the current API sources on the market is truly gas-tight; there is always a fair chance of intrusion of room air and thus water. Room air at 50% relative humidity and T = 20°C, which is considered a rather healthy environment for humans [44], contains about 1% V of water.[7] Second, once the source chamber is opened to ambient air, it will take weeks to get to 10 ppmV by flushing with ultra-pure nitrogen because water is strongly adsorbed onto the ion source walls and comes off again only slowly. The thing is, though: frequent and convenient opening of the source is in large part what makes API so appealing. Third, upon running an LC gradient containing e.g., 10% V of water, it will take even longer to get back to 10 ppmV or less. In essence, it is reasonable to assume that API sources are saturated with water. Ten ppmV mixing ratio for water is a very conservative estimate, 1‰V and more is rather typical. The same arguments apply to ambient ionization methods. The very moment the "hot" primary ion generating chemistry is cooled to thermal conditions (i.e., in domain 2, which is in this case an open environment), considerable mixing with surrounding air into the gas expansion (DART, FAPA, DAPPI) is to be expected. Ambient air contains up to 4%V [46] of water leading again to *at least* 10 ppmV mixing ratios of water within the chemically active matrix. In other words, gaseous water is ubiquitous in API.

Thermodynamic Aspects of Ion–Molecule Reactions

API chemistry is generally dominated by fast ion–molecule reactions. Why is this? First of all, we need to consider the rate constants of typical ion–molecule reactions. In the foreword of the most comprehensive compilation of ion–molecule rate constant data[8] Anicich concludes: "*From a glance at the 'Table of Reactions' it can be seen that there are only very few reactions that have measured rate constants between* $1 \cdot 10^{-10}$ cm^3 s^{-1} *and* $1 \cdot 10^{-12}$ cm^3 s^{-1}. *Most reactions are found to proceed at the collision rate or not at all.*" Second, we need to consider the dwell time of ions in the source (i.e., in domains 1 and 2). It has been experimentally shown ages ago [48], as well as recently again for a modern API source [49], that ions generated in the source enclosure may spend at least tens of milliseconds in this region; this holds true for almost all current commercial API sources. In fact, only the most kinetically energetic ion species make it to the inlet orifice in this time. The average ion needs up to several hundred milliseconds to finish the race; the actual range is of course strongly dependent on the source design. This time frame, along with the magnitude of typical ion–molecule reaction rates strongly suggests that full thermodynamic control of the ion concentrations present in the source is achieved. Time does not appear to be an issue, since all equilibria involved adjust much faster than the minimum dwell time. This holds true for bimolecular as well as termolecular reactions, at least when water or any other species present in the background matrix at ppmV mixing ratios (dopants, LC solvents) are actively involved.

Let us consider the proton bound water cluster reaction system as an illustration:

$$\left[H + (H_2O)_n\right]^+ + H_2O + N_2 \quad \rightleftharpoons \quad \left[H + (H_2O)_{n+1}\right]^+ + N_2$$

(Reaction14a, 14b)

[6]It appears as if this N_2 is not as ultra-pure: microscopic ice crystals are speculated to be transported with the N_2 gas stream, leading to quite high H_2O mixing ratios upon reaching warmer regions (Private communication 2013. Sascha Albrecht, IEK-7, Research Center Jülich, Jülich, Germany).

[7]Based on a saturation mass of water in air at T = 20°C of 9 g m^{-3} [45].

[8]This compilation covers more than 2300 references from the years 1936 to 2003 [47].

with N_2 standing as representative for a bath gas molecule acting as an unreactive third body collision partner.

Reaction 14a/Reaction 14b establish a highly dynamic chemical equilibrium. In this case and p and T = constant Equation (1) simplifies to Equation (2),

$$\left(\frac{\partial G}{\partial \xi}\right)_{T,p} = \Delta_R G = 0 \qquad (2)$$

with $\Delta_R G$ as Gibbs function of the reaction system, and $\xi = n_i/\nu_i$. Since the stoichiometric coefficients ν_i are always 1 in Reaction 14a/Reaction 14b we can substitute ξ with the molar amount n_i of the i^{th} component present. With a couple of simple rearrangements[9] and using standard thermodynamic conditions we get [40]

$$\Delta_R G^0 = -RT\ln K \qquad (3)$$

with $\Delta_R G^0$ as the molar standard Gibbs function and K the equilibrium constant. Figure 2 summarizes the above reasoning in a very simplified way.

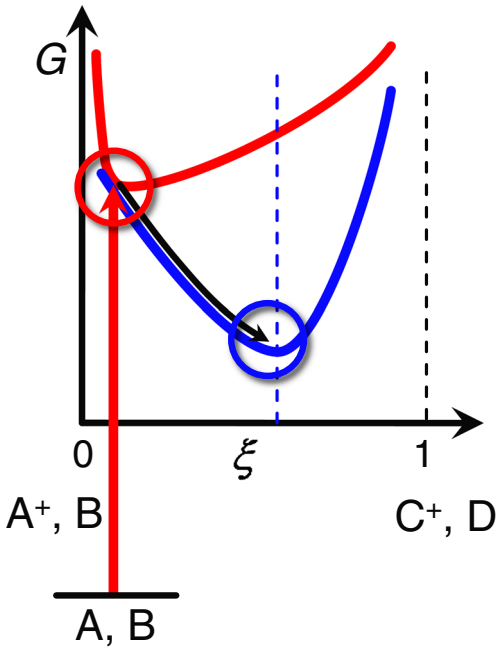

Figure 2. Simplified sketch illustrating thermodynamic versus kinetic control of an ion population distribution in a hypothetical $A^+ + B \rightleftharpoons C^+ + D$ equilibrium [41]. Red arrow: preparation of the initial ion population. Red curve: Dependence of the Gibbs energy on the progress of a reaction, which always leads to an ion distribution closely resembling the neutral analyte A mole fraction present in the source. Blue curve: dependence of the Gibbs energy on the progress of reaction, which either leads to an ion distribution closely resembling the neutral analyte A mole fraction in the source (red circle = kinetic control) or an almost equally distributed A^+ and C^+ ion population after equilibration (black arrow). The time required to reach the equilibrium position (blue circle, thermodynamic control) in cases where water, dopants, or LC solvents are involved (B), is generally less than 1 ms

From Thermodynamics to Kinetics

It becomes readily apparent why thermodynamic control and, thus, the calculation of the position of the respective equilibria is able to quantitatively describe the proton bound water cluster concentrations present in an API source: Reaction 14a is the apparently termolecular[10] production route of each cluster species. Before we proceed, we should take a brief look at the 'microscopic chemical event' representing that type of reaction. Recall: Whether or not a *bimolecular* reaction occurs as result of a collision event between two molecules A and B on a reaction coordinate with an activation barrier, is mostly a matter of less than a picosecond. This is very roughly the time required to "pass through" the critical configuration of the activated complex. The probability that *three* molecules collide within this time frame is statistically very close to zero, at least at AP. On the microscopic scale, a termolecular reaction is envisioned to occur in two elementary steps: (1) "Association" to form a comparably long-lived energized complex AB* and (2) "Deactivation" of AB* to AB through collision with a third body (M). Obviously, the overall efficiency of the last step depends significantly on the lifetime of AB*. Ion–molecule association complexes often exhibit lifetimes exceeding hundreds of picoseconds and more. It follows that there is a large time window for a third body collision to occur, which "bounces" $A^{+\cdots}B^*$ onto the reaction coordinate and removes energy leading to a bound molecule AB^+. In a very simple formal kinetic treatment, three[11] "true" elementary steps are considered. The first two determine the lifetime of the association complex and the third gives the rate for the subsequent deactivation and thus stable product formation

$$A^+ + B \rightleftharpoons A^{+\cdots}B^* \qquad (\text{Reaction14a1/Reaction14a2})$$

$$A^{+\cdots}B^* + M \rightarrow AB^+ + M \qquad (\text{Reaction14a3})$$

[9]OK, they are not that simple. It sounds better though—every PChem instructor uses such a wording one day or the other. Thermodynamics lectures provide ample opportunities to do so, as do quantum chemistry classes …

[10]From the IUPAC Compendium of Chemical Terminology [50]: "The number of reactant molecular entities that are involved in the 'microscopic chemical event' constituting an elementary reaction …"

[11]This approach is known as the Lindemann Mechanism. A rigorous modern treatment of such reaction systems builds on RRKM Theory [51]. This theory incorporates transition state geometries, quantum statistics, internal energies of the reactants, internal energy redistributions, and much more, and is thus much more accurate …

with the corresponding rate constants k(14a$_1$), k(14a$_2$), and k(14a$_3$). For the concentration of $A^{+\cdots}B^*$, stationary state conditions safely apply and the rate of formation of AB^+ becomes Equation (4):

$$\frac{d[AB^+]}{dt} = \frac{k(14a_1)\cdot k(14a_3)\cdot[M]}{k(14a_2) + k(14a_3)\cdot[M]}\cdot[A^+]\cdot[B] \quad (4)$$

If k(14a$_3$)·[M] >> k(14a$_2$), the rate of formation of AB becomes independent from [M] and, thus, independent from the pressure[12]; it reaches the *high pressure limit*. In this case Equation (4) may be simplified to Equation (5),

$$\frac{d[AB^+]}{dt} = k_{14}\cdot[A^+]\cdot[B] \quad (5)$$

with k_{14} as the pressure-independent second-order overall rate constant. It turns out that at 1 bar all cluster formation rate constants k(14a), $n = 1 \ldots 8$, are in the high pressure limit. The approximated Langevin model-based second order rate constants k(n → n + 1) account to $2 \cdot 10^{-9}$ cm^3 molecule^{-1} s^{-1} [52]. Using the experimentally determined molar standard Gibbs energies [17] for the individual cluster equilibria ($n = 1 \ldots 8$; Reaction 14a/Reaction 14b) yielding K (Equation 3) and the relation K = k(n → n + 1)/k(n + 1 → n), we get a set of rate constants which may be simply plugged into a differential equation solver such as ChemKed [53] along with the respective concentrations. A closer inspection of the bimolecular reverse rate constants k(14b) reveals that the lifetime of the individual cluster species spans several orders of magnitude: with k(8 → 7) = $1.3\cdot10^{-11}$ cm^3 molecule^{-1} s^{-1} we are again close to the collision limit (i.e., the lifetime of the $n = 8$ clusters is rather short); at 1 bar "short" translates to about 0.01 μs. On the other hand, k(2 → 1) is roughly 16 orders of magnitude(!) lower ($4.0\cdot10^{-27}$ cm^3 molecule^{-1} s^{-1}). Proton bound water dimers thus live much longer with respect to dissociation than with respect to growth, provided the background water mixing ratio is 1 ppmV or higher; in this case the pseudo first order formation rate k(2 → 3) is roughly $4\cdot10^5$ s^{-1}, which is again fast with a cluster lifetime of the order of μs.

Figure 3 summarizes this rationale in terms of the results of a kinetic simulation of the proton bound cluster system. In Figure 3a, a bar graph illustrates the equilibrated cluster population present at different water mixing ratios at atmospheric pressure. The calculated temporal evolution of the individual cluster species up to $n = 8$ is shown in Figure 3b. Coming back to the question we raised previously: "Do we have thermodynamic or kinetic control of the proton bound water cluster distribution present in an API source?" when we consider all key parameters together, such as the average ion dwell times in the API source exceeding tens of milliseconds—if not hundreds—and the rapid adjustment of the equilibrium concentrations (cf. Figure 3), it becomes apparent that full thermodynamic control is achieved.[13] In other words, the proton bound water cluster system readily shifts upon changes in temperature or background water concentration. This holds true for the entire high or elevated pressure regions.

Is Kinetic Control Possible at All in API Mass Spectrometry?

This question is "tricky."[14] Kinetic control can be accomplished in modern API mass spectrometers, but only with considerable effort, and only if participating neutral reactants are present below ppmV mixing ratios. In other words, regarding reactions involving e.g., water, dopants, or LC solvents, gaining kinetic control is virtually impossible, regardless of the ion source design. This was shown very early on, when compounds such as isobutene or NO were introduced as reagent gases for APCI [55] using a nozzle/skimmer sampling stage for essentially collision-free sampling. It was demonstrated that kinetic control was achievable only when the corona discharge region (domain 1) was placed at a distance of 0.5 mm from the sampling orifice. Recently, Kersten et al. [56] demonstrated that photoionization in close proximity to the downstream exit port of the inlet capillary of an API mass spectrometer leads to essential kinetic control of the recorded ion distribution. They used a custom miniature spark discharge VUV lamp irradiating the capillary gas flow directly. Kinetic control is achieved when the total reaction time of the generated ions with neutrals is less than 200 μs. The reaction system studied was the well described OH radical initiated gas phase degradation of 1 ppmV p-xylene (C_8H_{10}, *m/z* 106), which took place at AP in a dedicated large volume photoreactor designed for neutral radical driven atmospheric chemistry studies.

The API mass spectrometer employed for the analysis of the *neutral* reaction product distribution in the reactor effluent was fitted with an in-situ sampling stage, coupled directly to the inlet capillary. Photoionization took place either at atmospheric pressure upstream of the inlet capillary or inside the inlet capillary at a local pressure of about 300 mbar close to the capillary exit port, leading to 5 ms and 0.13 ms ion–molecule reaction times, respectively. After 30 min degradation time within the photo reactor, about 50%

[12]In other words, the collision rate of $A^{+\cdots}$ B* with M is larger than the unimolecular decay rate of $A^{+\cdots}B^*$. This is due to the fact that (a) the complex is "sticky" and (b) the collision cross section of an association complex is considerably larger than of a bound ion [52].

[13]Or we could search the literature and will certainly find this piece of text form the early 1980s: "The basic difference between API and EI or CI mass spectra is that API spectra normally show relative concentrations of ions under conditions of chemical and thermal equilibration, while EI and CI reflect relative rates of ionization reactions" [48].

[14]Deep Thought's reply in Douglas Adams Hitchhikers Guide to the Galaxy to the request of telling the answer to Life, the Universe, Everything [54].

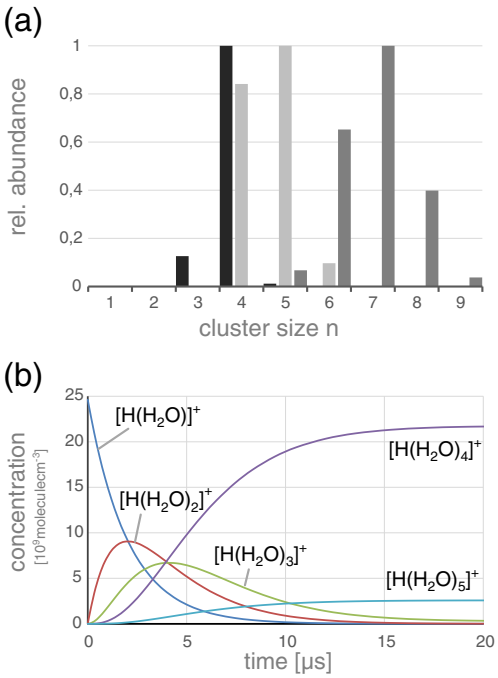

Figure 3. **(a)** Bar graph representing the relative proton bound cluster $[H + H_2O_n]^+$ distribution for n = 1 … 9 in the presence of 1 ppmV (black), 100 ppmV (light grey), and 1 ‰V (dark grey) H_2O mixing ratio, p = 1 bar. **(b)** Temporal evolution of the concentrations of proton bound water clusters when starting with $[H + H_2O]^+$ at a mixing ratio of 1 pptV as the only initial charged species present. Water background mixing ratio 10 ppmV, p = 1 bar. Clusters with n = 6 … 9 are not discernible on this scale

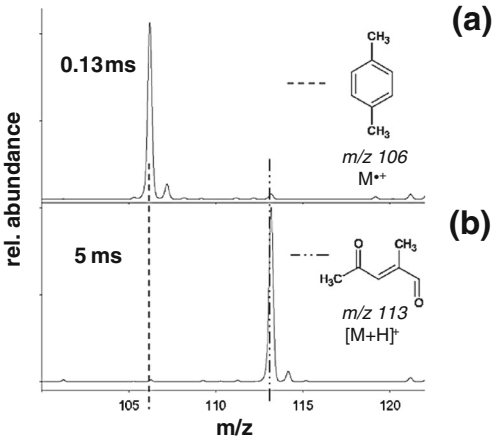

Figure 4. Photoionization mass spectra in the mass range 100 < m/z < 125, recorded upon sampling the reaction mixture from a large volume photo reactor, in which 1 ppmV of p-xylene was degraded for 30 min in the presence of OH radicals; **(a)** 130 µs ion–molecule reaction time in the inlet capillary; **(b)** 5 ms ion–molecule reaction time in the inlet capillary. All other parameters were held constant

of the xylene was transferred into products. A major branch in the xylene/OH system lead to the formation of a di-ketone $C_6H_8O_2$ (m/z 112, about 20% total yield), cf. Figure 4b).

The mass spectra recorded shown in Figure 4 are entirely different. Figure 4b represents the conditions of *thermodynamic control* (i.e., with all reactions reaching the respective equilibrium concentrations[15] leading to a spectrum with a strong signal at m/z 113 ($[C_6H_8O_2 + H]^+$). Note that no detectable signals relating to xylene were recorded. Naturally, the conclusion would be that all xylene has reacted to form the di-ketone. However, the spectrum shown in Figure 4a represents the case where the MS analysis is under *kinetic control*. In this case, reaction time is the key parameter that determines the ion concentrations present. The corresponding mass spectrum shows strong signals of xylene radical cations and only very small di-ketone signals. In this case, the conclusion could be that xylene is not degraded at all in the photo reactor. In fact, the only thing that has been changed is the number of reactive ion–molecule collisions within the MS detection system; every other experimental parameter was held constant.[16] Both of these observed results are readily explained: After 30 min degradation time, $C_6H_8O_2$ (~0.1 ppmV) and C_8H_{10} (0.5 ppmV) significantly exceed any other ion population generated in the detection system, which is at most in the ppbV range, if not much less. With ample reaction time, xylene radical cations generated via APPI act as proton donating dopants. Since ketones generally exhibit elevated gas-phase basicities, $C_6H_8O_2$ is quantitatively "titrating" away all xylene radical cations to form the respective protonated molecule, Reaction 15:

$$C_8H_{10}^{\bullet+} + C_6H_8O_2 \rightarrow [C_6H_8O_2 + H]^+ + [C_8H_{10}{-}H]^{\bullet} \quad \text{(Reaction15)}$$

On the other hand, if the reaction time is too short for chemical ionization reactions to proceed to any appreciable extent, the xylene radical cations are hardly depleted. $C_6H_8O_2$, on the other hand, is far less efficiently ionized directly with VUV light than xylene to form radical cations and, thus, only very small ion signals from this compound are observed. This example illustrates how thermodynamic control of reaction chemistry is the norm for API sources, with kinetic control only being observable under extraordinary conditions unlikely to prevail in conventional MS systems.

[15]In Thermodynamics reactions reaching completion cannot exist [41]. Rather, the equilibrium positions are "far to the left" or "far to the right", e.g., with 99.999 % product formation. The point though is that even much longer reaction times would not affect at all the ion concentrations present.

[16]The conclusion from such observations could be: "… 'Oh, that was easy,' says Man, and for an encore goes on to prove that black is white …" [56]

Conclusion

In the first part of this Critical Insight paper series, we have tried to address some of the mysteries of API mass spectrometry from a very simple and fundamental perspective: Which species are the major chemical players, which are simply spectators, and what is the impact of the physical environment on the prevailing ion–molecule chemistry?[17] We conclude that although kinetic control is achievable *in principle*, few if any modern API mass spectrometers currently feature a corresponding ion source design. Thus, virtually all instruments on the market generate ion population distributions within the source enclosure, which are thermodynamically controlled. It follows that cluster chemistry more or less dominates the *thermal* ion source processes. Since modern API mass spectrometers hardly detect clusters at all, the questions that readily come up are: Where are all the clusters going? and Do such processes affect the analyte ion–molecule chemistry as well? This will be a major focus in the second part of this paper series.

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[17]You may recall this approach from your General Chemistry textbook when setting up ICE (initial, change, equilibrium) tables for the calculation of equilibrium concentrations of weak acids and bases …

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