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An Ion Mobility Collision Cross Section Compendium

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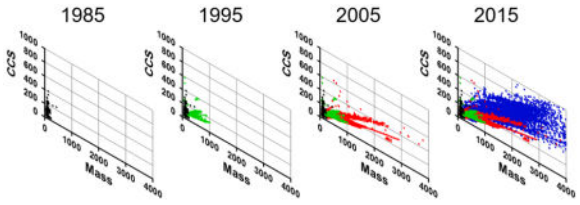
Abstract

In this review, we focus on an important aspect of ion mobility (IM) research, namely the reporting of quantitative ion mobility measurements in the form of the gas-phase collision cross section (CCS), which has provided a common basis for comparison across different instrument platforms and offers a unique form of structural information, namely size and shape preferences of analytes in the absence of bulk solvent. This review surveys the over 24,000 CCS values reported from IM methods spanning the era between 1975 to 2015, which provides both a historical and analytical context for the contributions made thus far, as well as insight into the future directions that quantitative ion mobility measurements will have in the analytical sciences. The analysis was conducted in 2016, so CCS values reported in that year are purposely omitted. In another few years, a review of this scope will be intractable, as the number of CCS values which will be reported in the next three to five years is expected to exceed the total amount currently published in the literature.

Graphical Abstract



Quantitative ion mobility methods have seen a resurgence of recent and significant interest due to the fact that in the past three years, a number of new and updated ion mobility technologies combined with mass spectrometry (IM-MS) have emerged as commercially-available instrumentation for routine chemical analysis. These have included updates to traveling wave instrumentation (TWIMS), new uniform field drift tubes (DTIMS) operated at both elevated [1] and reduced pressures (less than 10 Torr),[2–4] and a newly-developed ion trapping device operated in a mobility-selective mode (trapped ion mobility spectrometry, TIMS) [5–7]. Other ion mobility techniques including cyclic and extended path length

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Notes

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traveling wave devices are currently in development.[8,9] This recent and unprecedented commercial accessibility of IM-MS in combination with existing liquid chromatography and tandem MS functionality has provided powerful multidimensional separation capabilities to the greater research community,[10–13] which in turn has broadened the scope of applications and fields in which IM-MS is now making a significant impact.[14–19] Many of the contemporary challenges being addressed by IM-MS are grand challenges of our era of humanity.[11]

Ion mobility is generally utilized in one of three ways by researchers (Table 1): (1) as an added dimension of separation for increasing the peak capacity and partitioning the chemical noise from analyte signals of interest, (2) as an additional measurement for analyte identification and characterization, and/or (3) as a structural measurement technique, where the ion mobility information is used to infer some details regarding the structure (either primary or higher-order) of the analyte. The latter two strategies, analyte identification and structural measurement, are achieved by converting the ion mobility measurement (typically drift time), to an ion-neutral collision cross section value, which represents a fundamental property of the analyte comparable across different laboratories. Analyte identification and correlation can also proceed using the standardized mobility value, as has been achieved in the field of stand-alone ion mobility spectrometers utilized for chemical detection and screening,[20,21] although the fundamental meaning of the mobility measurement is more accessible when discussed in the context of the analyte CCS.

The Collision Cross Section

One of the contemporary challenges with interpreting the meaning of the CCS lies in the fact that it is not a true molecular cross section, but rather represents an observational property that averages all geometric orientations and interaction types (head-on, “glancing”, and “orbiting” collisions, multiple collisions within cavities of the analyte, *etc.*) across the experimental measurement time.[22–25] These effects include both contributions from the drift gas itself (momentum transfer and gas polarization effects) and contributions arising from the ion mobility experiment (temperature and magnitude of the electric field). Classically, the CCS determined from ion-gas collision measurements is referred to as the momentum transfer or diffusion CCS to specify the importance and dependence that the drift gas has on the resulting quantity being obtained.[26,27]

As a result of these contributions, the empirical CCS is a macroscopic quantity which is specific to the identity of the drift gas as well as the temperature and electric field used during the measurement,[28,29] and so by the strictest definition, CCS is not an intrinsic property of the analyte, although it is very closely linked to one (namely the microscopic cross section of the analyte). Mathematically, the CCS represents the area of a circle, and thus the structural information is “coarse-grained” in nature. While significant for small molecule studies, this level of granularity is less of an issue when probing coarse structural features such as domain-level information for protein assemblies. [30,31]

The CCS is a quantity that is now routinely obtainable from a variety of ion mobility experiments, and, although less frequently discussed, the CCS can also be obtained from

mass spectrometry experiments where gas collisions are present. Mass spectrometric methods utilized for measuring CCS have included pressure correlated ion loss studies in magnetic sector,[32–34] triple quadrupole,[35,36] and time-of-flight instruments;[37] ion relaxation times in an ion trap;[38] and peak width analysis from ion cyclotron resonance measurements.[39,40] Ion mobility methods currently provide the most precise measurements of the CCS, with precision being linked to the experimental certainty in all of the parameters which govern the IM separation, such as the gas temperature, electric field, gas number density (*via* pressure and temperature) and the geometric distances within the instrumentation. As such, uniform field drift tubes (DTIMS) and differential mobility analyzers (DMA) afford the highest CCS precision since experimental quantities in these techniques can be well-characterized. It should be noted here that precision and accuracy are important distinctions, as very reproducible CCS values can now be obtained (better than 2%),[2,41] but their accuracy cannot be validated without comparing the ion mobility results to CCS measurements obtained from other techniques, which at this time are still in development.[42–44] Despite these standing questions regarding the accuracy and meaning of the CCS, it is clear that there is immense value in reporting a standardized fundamental property of an analyte in the form of a CCS which is both highly-reproducible and now readily-accessible by a large number of researchers.

Recent publications have utilized an elegant nomenclature for CCS reporting whereby the measurement technique is denoted as a superscripted prefix, while the drift gas is specified as a subscripted suffix, for example, $^{DT}CCS_{N2}$ to denote a nitrogen CCS value measured from a drift tube instrument.[45–48] This nomenclature is summarized in Table 2 along with specific recommendations for the instrumentation shorthand. Given the oftentimes ambiguous nature of the experimental context in which CCS values are reported, the nomenclature formalized in Table 2 is recommended for future use in the field.

Significant CCS Contributions

The emerging importance of CCS to support contemporary analytical trends is evidenced by the fact that over half of the over 24,000 canonical CCS values reported between 1975 and 2015 has been published within the last five years (Figure 1A). Examining the histogram in Figure 1A indicates there was an initial surge of CCS values reported between 1995 and 1999 which was largely in response to the introduction of ESI and MALDI ionization techniques, followed by a decade of relatively few new CCS values being reported (2000–2009). Starting in 2010, the number of CCS values reported increased drastically, which is interpreted as being a direct response of the introduction of new ion mobility techniques, including commercial TWIMS technology in 2006,[49] confining RF DTIMS in 2010,[50] and DTIMS integrated with ion funnels, initially reported in 2005 and commercialized in 2014.[2,51]

Major contributions from specific laboratories are noted in Figure 1B and include several large-scale studies from Clemmer and coworkers examining electrosprayed peptides and proteins in helium (*ca.* 4200 values),[52–55] contributions from Bowers and coworkers on hydrocarbons and carbon clusters (*ca.* 400 values),[56–59] studies from Jarrold and coworkers investigating carbon, silicon, and palladium clusters (*ca.* 550 values),[60–63] contributions

from Russell and coworkers reporting singly-charged CCS values of MALDI generated peptides and proteins (*ca.* 650 values);[64,65] TWIMS and DTIMS studies from Pagel and coworkers investigating both helium and nitrogen CCS for carbohydrates (*ca.* 1300 values),[45,66,67] work from McLean and coworkers which include a number of lipid, peptide, and carbohydrate CCS values in both helium and nitrogen (*ca.* 1000 values),[2,68,69] and recent TWIMS work from Astarita and coworkers reporting nitrogen CCS values for both lipids and metabolites (*ca.* 450 values).[70,71] The largest single quantitative ion mobility survey to date represents the *ca.* 8,700 nitrogen CCS values published by Smith and coworkers for tryptic peptides in support of proteomics studies.[72] While the early studies have focused on obtaining structural information through the measurement of the CCS, several of the recent contributions have been purposed as cross sectional databases in support of analyte characterization. The motivation for utilizing CCS as a molecular descriptor (*c.f.*, Table 1) is an emerging application area in the field of analytical chemistry. Additionally, the high quality CCS data from the Clemmer[73] and Bush laboratories[41,50,74] are routinely used for calibrating ion mobility instrumentation.

While only major studies are highlighted here, the majority of contributions to the CCS canon (75%) have come from smaller studies which report 50 or fewer CCS values (Figure 2). In fact, there are only three individual studies which have reported over 1,000 CCS values and thus would be considered large-scale surveys,[54,55,72] underscoring the fact that the reporting of quantitative ion mobility measurements is predominantly an interlaboratory initiative.

Drift Gases Represented

While measurements obtained in helium and nitrogen represent the vast majority of the CCS values reported (95%, *c.f.*, Figure 1), there have been a few quantitative studies conducted in alternative drift gases, most representing the classic atomic and small molecule studies compiled by Mason and coworkers during the early developments of analytical ion mobility,[75–78] but also early work from Hill and coworkers exploring CCS differences of small peptides and drug molecules in helium, nitrogen, argon, and carbon dioxide.[79] Recent studies which explicitly report CCS values in alternative drift gases include measurements of ammonium in helium, nitrogen, argon and carbon dioxide from Viehland and coworkers,[80] the combined DTIMS and TWIMS study from Barran and coworkers investigating myoglobin in helium, nitrogen, argon, and neon,[81] DMA measurements of CCS in air from both de la Mora and coworkers[82] and Hogan and coworkers,[83] and DTIMS work from Fjeldsted and coworkers exploring the CCS differences of pesticides in a variety of drift gases including helium, nitrogen, carbon dioxide, nitrous oxide, argon, and sulfur hexafluoride.[84]

The sparse amount of CCS data reported for gases other than helium and nitrogen is largely a combined result of both technical challenges with operating under different drift gas conditions (instrument tuning, pressure gauge calibration issues, and uncertainty with calculating the CCS from measured drift times), as well as fundamental difficulties with interpreting the structural meaning of CCS values obtained using gases other than helium. The typically better correlation of helium CCS values to theoretical results is primarily a

consequence of the lower contribution of ion-neutral polarization effects in atomic helium (α=0.21 Å^3) as compared to diatomic nitrogen (α=1.74 Å^3) and other neutral gases (*e.g.*, argon, α=1.64 Å^3; carbon dioxide, α=2.91 Å^3),[79,85–87] although it should be noted that significant and recent efforts have been made in improving the fundamental theories used in predicting nitrogen-based CCS values from candidate structures.[25,26,88,89] In addition to the better theoretical correlation of helium CCS, there is also some evidence that helium offers analytical benefits in reducing mass-mobility discrimination and improving ion transmission in dispersive (DTIMS and TWIMS) ion mobility instrumentation.[90,91] The choice of nitrogen as a drift gas stems from practical considerations of cost and availability, fundamental considerations regarding nitrogen's resistance to electrical discharge (dielectric breakdown) and analytical improvements in resolving power due to the longer residence time of ions (*i.e.*, lower reduced mobility values) within the ion mobility experiment.[92] While these attributes are shared by other drift gases such as argon and carbon dioxide, their use in quantitative IM research has not yet been significantly explored. It is anticipated that the meager quantitative IM data currently available for alternative gases represents only a temporary deficiency as the instrumentation and CCS measurement capabilities to support different drift gases are now becoming widely available, and evidence is mounting in support of the analytical benefits of conducting IM separations in other drift gases such as argon and carbon dioxide.[93–97]

Composition of Measurements

An analysis of the composition the CCS values published from 1975 to 2015 is presented in Figure 3 for a few select categories. With regards to instrumentation (Figure 3A), most (87%) of the CCS values represent measurements conducted in DTIMS instruments, which include both elevated[98–102] and reduced pressure DTIMS instrumentation,[103–110] as well as instrumentation utilizing electric field-mediated ion focusing strategies such as periodic DC,[111,112] confining RF,[4,50] and electrodynamic ion funnels.[2,51,113] A cursory comparison of the measurements themselves (not shown) indicates there is no significant differences between the CCS values obtained using these different modes of DTIMS operation, suggesting these focusing strategies do not perturb the resulting CCS. Because DTIMS still exhibits the highest precision when measuring the CCS and the direct relationship between drift time and cross section allows broad scale CCS determination of mixtures, it is no surprise that DTIMS has contributed to the majority of values published to date. TWIMS values obtained from calibration represent 9% of the CCS values,[114–117] while the remaining values are from other IM techniques such as DMA[82,83] and TIMS.[118–121]

Regarding the selection of drift gas (Figure 3B), there are slightly more CCS values being obtained in nitrogen (49%) as compared to helium (46%), with reporting of nitrogen-based CCS values being a recent analytical trend in the field (*c.f.*, Figure 1A). Measurements in ambient air comprise 3% of the CCS values, which are from elevated pressure DTIMS and DMA studies. The remaining 2% of values are for measurements conducted in argon (0.5%), carbon dioxide (0.3%), oxygen (0.3%), neon (0.2%), nitrous oxide (0.2%), and others (0.5%). Specific motivations for drift gas selection are discussed in the previous section.

Figure 3C indicates that the majority of CCS values are for low charge-state cations (+1, +2, and +3 ions, collectively representing 78% of all values reported), and thus anion CCS values are currently underrepresented, comprising only 8% of the total body of work. This predominance of positive ion data is expected given that MS-based studies are preferentially conducted in positive ion mode. Most of the anions CCS values reported are from two recent carbohydrate studies, one on chemically-released glycans and corresponding ion fragments generated in source,[67] and another reporting negative ion CCS values on dextran and pullulan oligosaccharides.[122] Remaining anion contributions represent the classic DTIMS studies on atomic and molecular clusters,[57,63,123] and recent negative ion measurements for proteins,[124] lipids,[1,71] and metabolites.[70,125] The primary ionization method used in the quantitative measurement of the CCS is ESI (87%, not shown) which tends to produce primarily +2 ions for tryptic peptides.[126] As tryptic peptides represent the majority of CCS measurements reported in the literature (*vide infra*), it is no surprise that there are more +2 ions than any other charge state. Laser-based ionization (MALDI and LDI) which produce mainly +1 ions in positive ion mode comprise only 11% of the CCS values (not shown). Higher charge state cations (+4 or greater) comprise 14% of the CCS values reported, which is in line with the number of protein ion CCS values represented in the analysis (9% of the total, not shown).

Finally, in Figure 3D, an analysis of the contributions made within specific chemical classes reveal the majority of CCS values reported in the literature are for peptides and proteins (70%), with carbohydrates (8%), inorganics (*e.g.*, clusters, nanomaterials, and salts; 8%), and other small molecules (*e.g.*, hydrocarbons and metabolites; 6%) representing the remainder of values. The focus on peptide and protein work can be rationalized as being a result of continued efforts for adapting ion mobility technologies to proteomics workflows,[127–129] but also a practical consequence of both the ease of generating large pools of peptides derived from enzymatic digestion[130] and the fact that the structural and charge-state heterogeneity of proteins necessitates the reporting of many CCS values for a single protein. [131–134]

To summarize the observations in Figure 3, most quantitative ion mobility studies to date have used DTIMS for peptide and protein analysis, with an approximate equal number of measurements represented in both helium and nitrogen drift gases.

Chemical Space Represented by IM-MS Analysis

Figures 4 and 5 projects all of the canonical CCS values as a function of the ion mass, for helium and nitrogen-based ion mobility measurements, respectively. The scattering of measurements (lower panels) are noticeably different in both gases, underscoring the fact that different analytes and charge states are represented in each type of gas. For example, a larger percentage of helium CCS values are singly-charged (37%) compared to a smaller percentage of singly-charged values in nitrogen (13%). Nitrogen CCS values also contain a significant number of triply-charged measurements (34%), in contrast to helium CCS values, which are comprised of only 14% triply-charged CCS values. This is one reason for the more prominent clustering of higher charge-state measurements in nitrogen (Figure 5, lower panel). There are also a significant number of CCS values for atomic and molecular clusters

(carbon, silicon, and inorganic salts) which are unique to the helium CCS measurements, resulting in the trends prominently observed at low CCS (Figure 4, lower panel). Nitrogen CCS values are larger in magnitude than helium values due to the higher momentum contribution of the nitrogen molecule as well as the stronger polarization which in turn leads to temporally-extended ion-neutral interactions in the IM experiment.

The central panels in both Figures 4 and 5 project the average mathematical fits to specific biochemical classes based on a power-law relationship.[2] Only the fits to singly-charged analyte is shown, and fits are not extrapolated beyond the range of measurements. The total chemical occupancy of all measurements is illustrated by a 95% data inclusion area (grey shaded region). The general conformational ordering of biomolecules observed here qualitatively correlates to the gas-phase structural trends noted from previously studies, that is, lipids adopt more extended structures in the gas-phase than peptides and carbohydrates.[2,135,136] The quantitative differences observed between helium and nitrogen are a consequence of evaluating the CCS values corresponding to different analytes in each figure. This can be seen by examining the biochemical class compositions which are noted in the central panel of each figure, where for example, significantly more peptides and proteins are represented in nitrogen (80%) than helium (67%).

The 3-dimensional surface plots and associated histograms projected on the top panels in Figures 4 and 5 illustrate the distribution of CCS values reported for both helium and nitrogen drift gas. Overall, the analytes surveyed from both gases fall within a similar mass window between 500 to 1500 Da with more values at lower mass reported for helium than nitrogen. As many of the helium measurements are from earlier work in the field and represent singly-charged analytes, it is no surprise that the overall coverage concerns lower mass analytes.

CCS Coverage over Time

Figure 6 compares the number of CCS values reported over the past 40 years as they correlate to mass. This analysis reveals that, as expected, the focus of quantitative ion mobility studies has shifted over time to higher mass due to improvements in technology and methods used to desorb, ionize, and stabilize large analytes such as biomolecules. Prior to the widespread use of soft ionization methods (*ca.* 1995), the average mass of ions for which CCS values were being reported was less than 100 Da,[75–78,137–141] and in the decade following the adoption of MALDI and ESI (1996–2005) in research instrumentation, a broad range of ion masses up to *ca.* 2500 Da were investigated, though the majority of measurements were centered on low mass studies around 300 Da. In the past decade (2006–2015), the average ion mass was approximately 1000 Da and represents predominately peptide CCS values, however significant efforts were also made for reporting CCS values of lower mass ions centered around 400 Da, the latter representing analytical interests in short-chain carbohydrates,[142–147] metabolites,[70,125,148–151] and drug-like molecules.[84,87,89,152] Figure 6B contains the distribution of CCS reporting with analyte masses extending up to the megaDalton range, which illustrates the recent analytical trend of utilizing quantitative ion mobility methods to study the structure of large protein assemblies,[50,124,153–159] some of which are annotated in the figure. These studies specifically target IM-based measurements

towards the interpretation of molecular structure. Note that the vertical scale in Figure 6 is the same in both panels, however, the bin size is increased in Figure 6B (from 50 Da to 10 kDa) to accommodate the broader mass range being projected. A final observation to make from Figure 6A is that the bimodal distribution observed over the past five years (2011–2015) closely mimics the analytical trend observed within the largest chemical database, PubChem,[160,161] where chemical entries have, over time, shifted to focusing on lower mass analytes while the total number of entries in PubChem currently exhibits a bimodal mass distribution.[11]

The bubble plot projection in Figure 7 compares the number of CCS values reported over time with respect to specific analyte classes and types. In this projection, the bubble size correlates to the number of values reported for each corresponding year. Early quantitative IM studies focused on atomics and small molecules. A significant number of the small molecules CCS values consists of aromatic hydrocarbons.[98,119,139,162–164] Starting in the 1990s, interest in inorganic compounds (metal salts, atomic and molecular clusters) began to emerge. Very few inorganic compound CCS values were reported between 2000 and 2010, with a resurgence of interest starting in 2013 which were primarily focused on gaining fundamental insights into the structures of inorganic salt and metal clusters.[83,165–169] Protein CCS values were initially reported in the late 1990's by the Jarrold, Clemmer, and Bowers groups,[170–173] with sparse numbers of measurements reported thereafter for several years. From the year 2000 onward, efforts in the field were largely concentrated on biological molecules. A significant number of peptide and protein CCS values started appearing again in the literature in 2007. The large blue bubble in Figure 7 corresponds to the 8676 peptide cross sections published by Smith and coworkers in 2010 in support of developing theoretical methods for predicting the IM drift time based upon the primary amino acid sequence.[72] While most of the CCS values have been for tryptic peptides, there is recent and significant efforts being made in the quantitative IM analysis of structurally-interesting peptide and protein classes, including helical peptides,[174–176] metalloproteins,[177–180] intrinsically-disordered proteins,[181–184] metamorphic proteins,[185,186] amyloids,[187–194] and membrane-bound proteins and assemblies.[117,195–198] The last three years has seen a balance of cross section reporting across most of the chemical classes, including lipids and carbohydrates. The exception is nucleotide CCS values, which, aside for the 2009 study from McLean and coworkers,[68] have been published in small numbers spread across several studies and years, and currently comprise about 1% all CCS values reported.[153,199–209] This observation is reflected in the fact that while many of these IM-based biomolecular studies have coincided strongly with developments in MS-based lipidomics, glycomics and metabolomics, the role of mass spectrometry related techniques in genomics research is, and has always been, relatively small.

Not shown in Figure 7 are the large number of studies which have focused on synthetic polymers,[210–220] which, like nucleotides, have seen a small but gradual number of CCS value reporting since the initial measurements by Bowers and coworkers in the late 1990s.[221–225] Several recent polymer studies have focused on reporting CCS values for dendrimers.[226–228], and polymeric supermolecular assemblies utilized in molecular sensing, catalysis, and advanced materials applications.[229–237] Overall, synthetic polymers comprise about 1% of the total number of CCS values reported to date, virtually all of which are

measured in helium drift gas or are calibrated to helium-equivalent values. Also not reflected in the analysis presented in Figure 7 are the recent interests in characterizing natural products by IM-MS based CCS measurements.[69,116,238–240] Many natural products contain complex and unusual scaffolds which motivates their study by a structurally-selective technique such as IM-MS, however, natural products are conventionally classified based on bioactivity rather than structure and as such molecules which can be considered natural products are represented in virtually all of the chemical classes delineated in this review. A similar issue is seen in metabolites (not shown) which is a classification that includes small peptides, carbohydrates and lipids. Finally, there are a number of CCS measurements which cannot easily be classified into a given chemical class category, such as compounds derived from chemical synthesis.[241–245] It is anticipated that additional trends in the analysis of chemical classes not described in this review will become evident as the field of quantitative IM continues to grow.

CONCLUDING REMARKS

This current analysis of all collision cross section values published into the canonical literature from 1975 to 2015 reveals both important analytical trends in the field, such as the focus on biomolecules and drift tube studies, and also avenues where future efforts will make a significant impact. These future analytical prospects include, (1) the use of emerging ion mobility methods and mass-spectrometry based techniques for validating the accuracy of CCS measurements, (2) quantitative IM experiments exploring alternative drift gases such as carbon dioxide and argon, (3) overlapping analyte studies which explicitly compare fundamental differences across different gases, charge states, and polarities (4) anion studies to test whether or not conformational ordering observed for cations is retained in negative ion mode, (5) quantitative studies of underrepresented chemical classes such as nucleotides, lipids, and synthetic polymers, and (6) comprehensive CCS mapping of suites of analytes (*e.g.*, chemical classes, pharmacologically-active, or disease-implicated) in support of unknown identification and characterization by means of searching databases and libraries. In terms of the immediate analytical impact of this current work, the compilation of CCS measurements will provide a basis for correlating future measurements to the canonical literature, enable large-scale studies of the quantitative relationships within chemical classes and across different drift gases, and serve as a basis for developing predictive methods for CCS chemical space occupancy. Importantly, the compilation of these measurements will provide a foundation for supporting future efforts aimed at utilizing the CCS as an additional metric for analyte identification, with correspondence to other analytical measurements such as exact mass, tandem MS data, and chromatographic retention time. Given the rapid growth now being seen in the field of quantitative ion mobility, many of the analytical prospects outlined in this review will likely be realized in the next few years.

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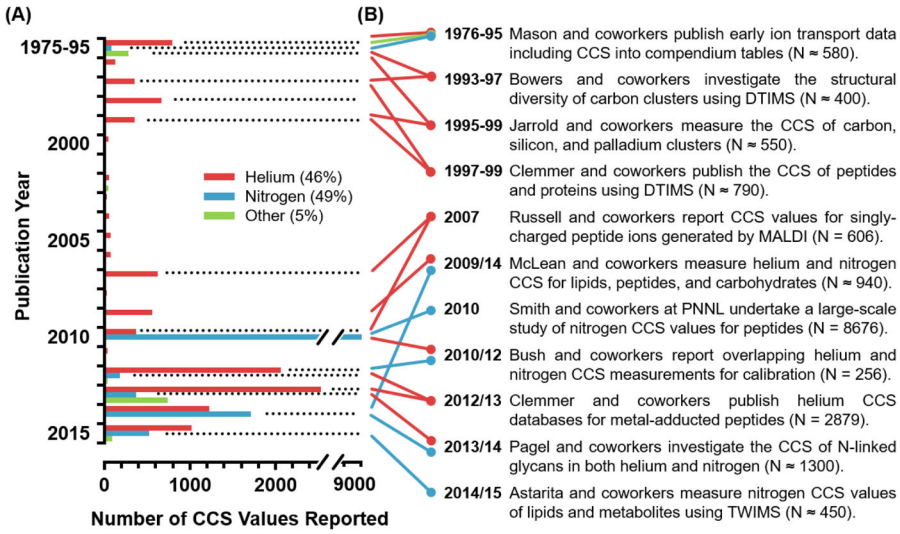

Figure 1.

(A) The number of CCS values published over the 40-year span between 1975 and 2015. The drift gas used in the measurement or calibration is specified for each year bin. (B) The laboratories and studies which have made significant contributions in terms of number of values reported.

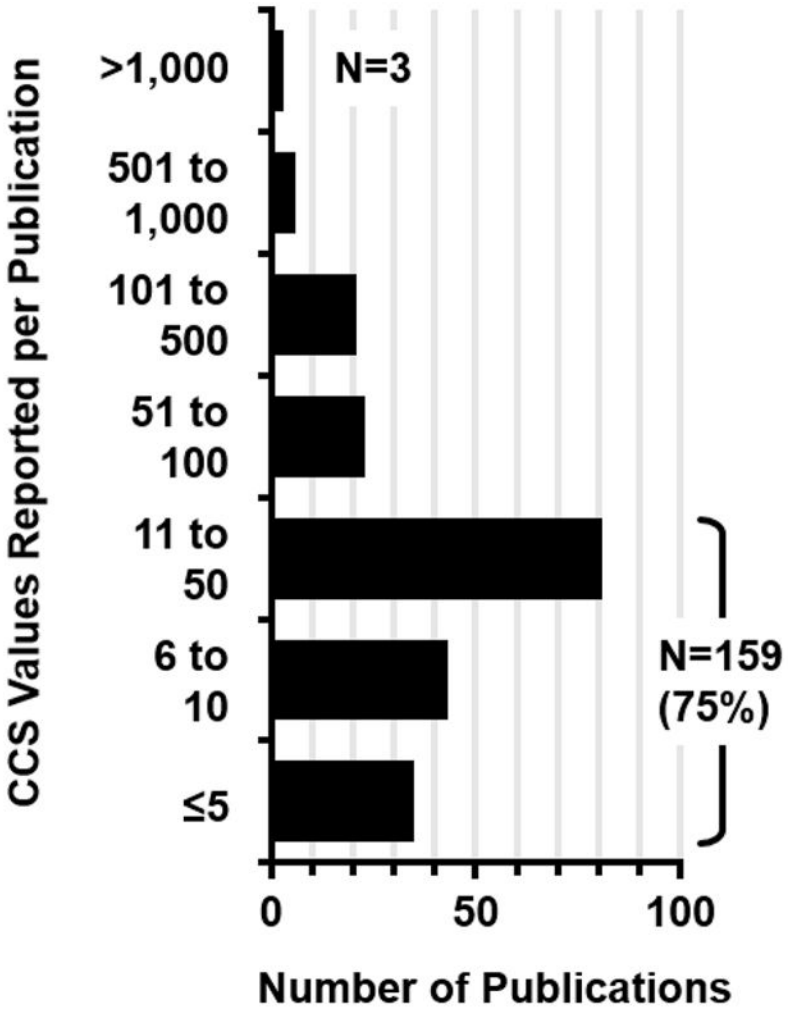

Figure 2.

Histogram illustrating the number of CCS values which are reported per publication. The bracketed bins draw attention to the fact that most of the CCS measurements have come from smaller studies reporting 50 or fewer cross section values.

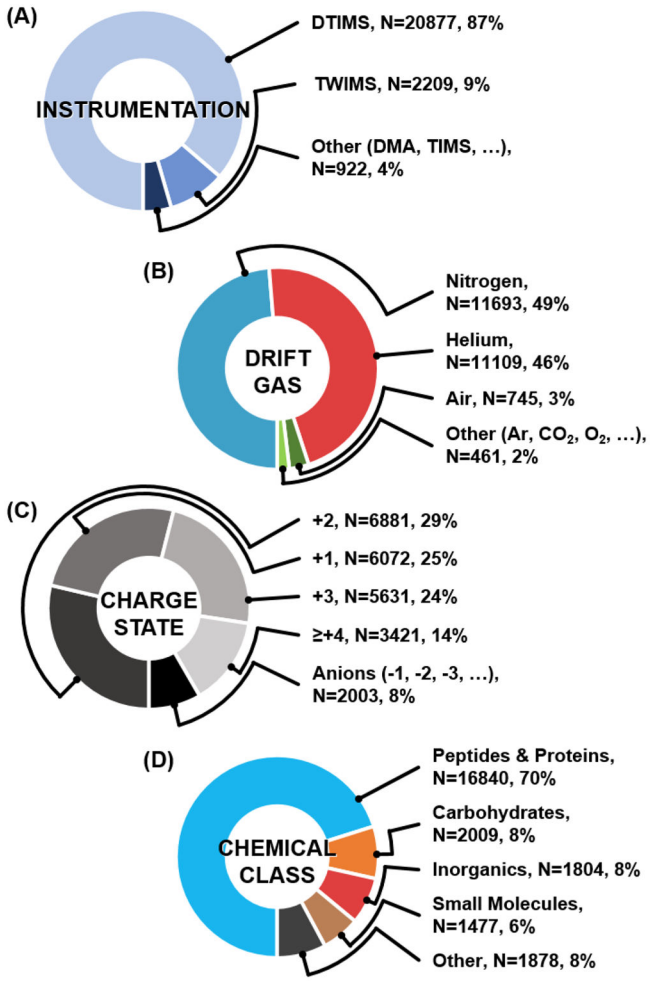

Figure 3.

Composition of CCS values with respect to (A) the ion mobility instrumentation used, (B) the drift gas, (C) specific charge state reported, and (D) the chemical classes investigated.

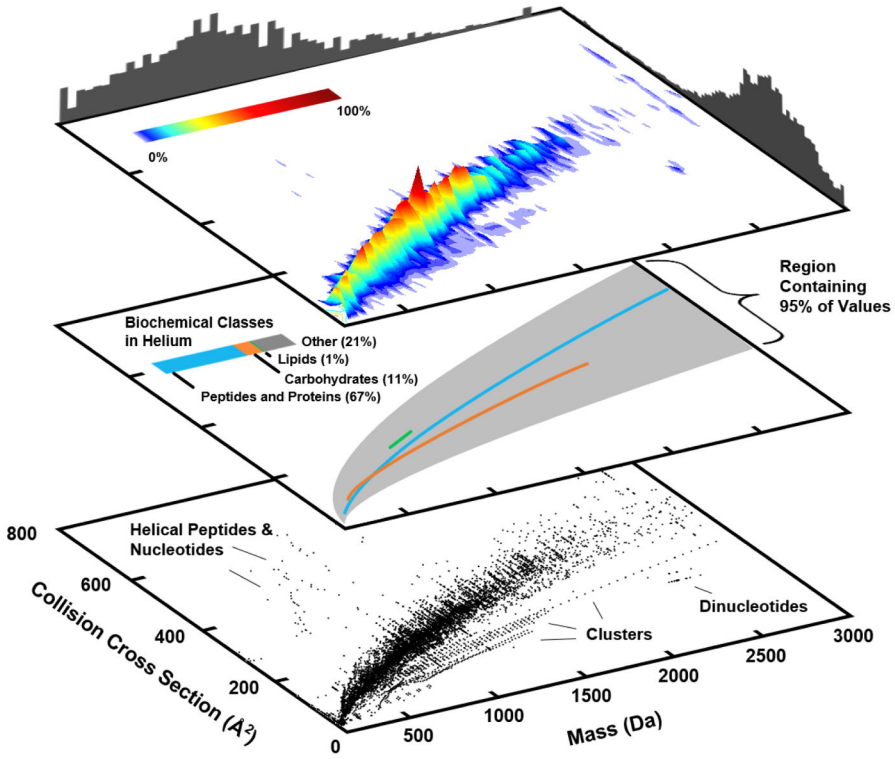

Figure 4.

(lower panel) Helium-specific conformational space plot which projects helium-based CCS values as a function of the analyte mass. (middle panel) The composition and chemical space occupancy of specific biomolecules. (top panel) A 3-dimensional surface plot illustrating the regions of highest density in terms of the numbers of CCS values.

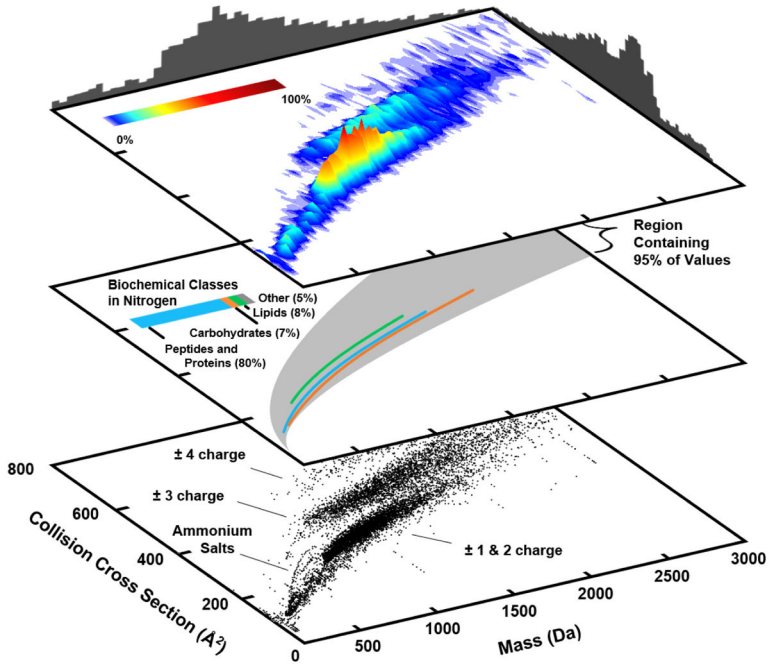

Figure 5.

Nitrogen-specific conformational space plot which projects nitrogen-based CCS values as a function of the analyte mass, along with (middle panel) the biomolecular composition and occupancy and (top panel) the 3-dimensional surface density plot of CCS values reported.

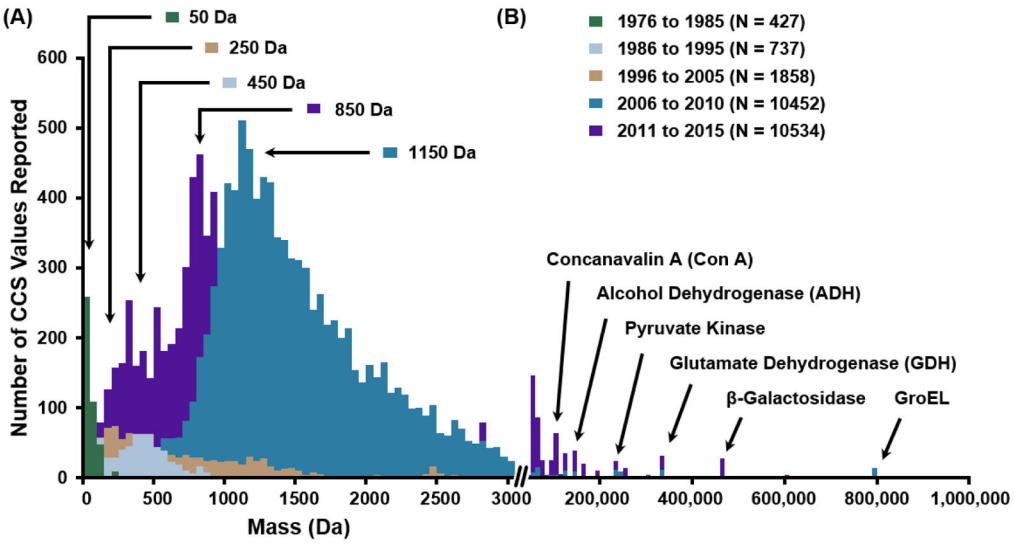

Figure 6.

Histogram illustrating the number of CCS values reported as a function of mass with data sets delineated into specific timespans. Panel (A) contains the histogram for low mass analytes below 3000 Da, with arrows denoting the approximate mass where each distribution exhibits a maximum. Panel (B) contains the histogram for high mass analytes above 3000 Da, with labels calling out select protein assemblies which have been studied. Note that the vertical scales are the same in both panels; however, the bin size in panel B (10 kDa) is different than the bin sized used in panel A (50 Da).

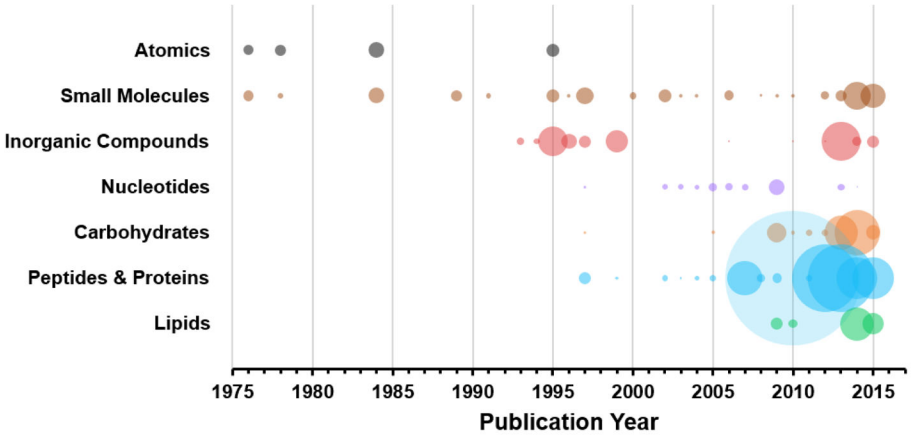

Figure 7.

Bubble plot projecting the number of CCS values reported over time for the top 7 chemical classes represented. The size of each bubble encodes the relative number of CCS values for each respective year.

TABLE 1

Three key analytical uses of ion mobility

Analytical Use of Ion Mobility	Description	Additional Requirements	Example Application Areas
1. Chemical Separation	Partition signal from chemical noise and increase peak capacity of the analysis	None	Detection of Illicit compounds (*e.g.*, drugs and explosives) and screening of exogenous metabolites (*e.g.*, pesticides and industrial chemicals)
2. Analyte Identification and Characterization	Use CCS measurement to characterize unknowns by correlation	Reference values from databases and libraries incorporating normalized drift times, reduced mobilities, and/or CCS	Emerging omic and small molecule discovery initiatives
3. Structural Analysis	Utilize the experimental CCS to infer structural information	Computational methods to link theoretical structure(s) to the experimental CCS	Insights into protein complex arrangements and structure

TABLE 2

Formalized nomenclature for reporting CCS measurements in the context of the technique and drift gas utilized

CCS Measurement Technique	Technique Shorthand [a]	Nomenclature for CCS Reporting [b]
Drift Tube Ion Mobility Spectrometry (DTIMS)	DT	$^{DT}CCS_X$
Traveling Wave Ion Mobility Spectrometry (TWIMS)	TW	$^{TW}CCS_X$
Trapped Ion Mobility Spectrometry (TIMS)	TIMS	$^{TIMS}CCS_X$
Differential Mobility Analyzer (DMA)	DMA	$^{DMA}CCS_X$

[a] Only the four major ion mobility techniques which report CCS are listed.

[b] X denotes the drift gas or drift gas equivalent for calibrated values (X = He, N2, Ar, CO2, *etc.*)