

[0097] In addition to the aforementioned to the advantages realized through the use of hyperbolic field focusing, a number of other aspects of the present invention are described below. These additional aspects of the present invention involve a number of instrumental and method refinements resulting in improved apparatuses and methods for separating and analyzing ions in a high-pressure gas. The resulting methods and apparatuses enable analyses having high sensitivity for charged species while maintaining resolution comparable to that achieved in moderate resolution drift tubes known to the art while providing an easily constructed and implemented solution. The apparatus comprises one or two electrodes to which voltages are applied, spaced apart from an aperture plate which samples charged particles. Once sampled using the aperture plate, the ions may be detected by a conventional IMS detector (consisting of an electron multiplier and associated electronics) or a mass spectrometer.

[0098] Ions can be produced by any number of means including in part electrospray ionization, laser ionization, photoionization, electron ionization, chemical ionization, electric field ionization, surface ionization, radioactive ionization, discharge ionization, multiphoton ionization, etc., with the chosen method of ionization being matrix assisted laser desorption ionization (MALDI). The laser is the preferred example of an ionizing beam excitation. In one embodiment of the invention ions are produced by MALDI in a well-defined ion packet thereby eliminating the need for an additional means of gating, i.e. with a Bradury-Nelson gate. Once formed, ions are made to flow by a suitable arrangement of electric fields produced by one or two easily manufactured electrodes. The ions are then separated by mobility, sampled through an aperture plate and either focused into the source region of a time-of-flight mass spectrometer to enable mass analysis of the mobility separated ions, or focused onto a conventional IMS detector to enable mobility analysis of the exiting ions. The resolution attainable with an ion mobility spectrometer is determined by a combination of the effect of a finite pulse width of originating ions and the total potential drop experienced by the ions. In one embodiment of the present invention, MALDI is the preferred ionization method and the ion packet formed is of extremely short duration (4 nanosecond laser pulse width) and composed of a limited number of ions (space charge effects on resolution are negligible). Therefore, the resolution of a MALDI/IMS spectrometer is diffusion limited and predominantly a function of the applied potential (experimentally verified by observing a constant increase in resolution with applied voltage), determined by the discharge properties of the buffer gas employed. It is an object of the present invention to maximize the sensitivity of the IMS drift cell while maintaining the resolution within the diffusion limited regime and simultaneously constructing the apparatus in a simple manner, i.e. with a minimum number of electrodes (1 or 2).

[0099] An additional advantage realized with the use of MALDI ionization is its amenability to the analysis of large molecules, particularly biologically important molecules. MALDI is a rather gentle ionization technique, thereby minimizing fragmentation of large biomolecules, particularly proteins and nucleic acids. This facilitates elucidation of sequence and structure. Analysis of such samples is simplified by minimizing fragmentation, resulting in less cluttered spectra. Other soft ionization techniques such as

electrospray ionization enjoy similar advantages. When mass spectrometry is used as a detection scheme, a two dimensional pre-selection of ion is realized; one based upon simplification of ion population at the outset, and another based upon the use of mass spectrometry in addition to ion mobility.

[0100] Also described herein are instrumental improvements in the detection architecture of an ion mobility spectrometer. As used herein, the ion detector refers to any instrumental apparatus in fluid and electronic communication with the sample ionization and drift cell instrumentation and which ultimately outputs data which characterizes the sample under analysis. The ion detector may be a conventional aperture grid/collector/amplifier assembly typically used in mobility analysis. Alternatively, it may also comprise more complex instrumentation and electronics such as that which may enable mass spectrometric analysis of the chemical species separated by mobilities. In the latter case, a consistent problem with prior art instruments in throughput losses that occur in going from a high pressure stage (ion mobility drift cell) to a low pressure stage (the mass spectrometer). Instrumental modifications are described herein that represent improvements in ion throughput in comparison to conventional instruments.

[0101] FIG. 16 is a schematic view of a spectrometer 1. Spectrometer 1 comprises an ion mobility cell 2, fed from an ion source 3. A lens system 4, focuses ions into a housing having a detector 5, and an orthogonal time-of-flight mass spectrometer 6. A laser 7 may be used as apart of the ion source 3 in selected applications. The laser generates gaseous molecular ions from a solid matrix/analyte sample introduced into ion mobility cell 2 through vacuum interlock 8 and deposited on probe tip or multiple well plate 9. The small packet of MALDI formed ions drift in a buffer gas under the influence of a suitable electric field applied between back electrode 10 and aperture plate 11. Following ion mobility separation in ion mobility cell 2, ions are sampled through a 200-500 micron diameter aperture 12. With a mobility cell buffer gas pressure of 1-10 Torr helium the analyzer chamber 14 is kept below  $1 \times 10^{-5}$  Torr by a small high vacuum pump 15. Ions exiting aperture 12 are focused by lens system 4 onto either detector 5 to record the ion mobility arrival time distribution or into the time-of-flight source 13 where arriving ion packets are pulse focused orthogonally into a 20 cm long flight tube 16. Mass spectra are then recorded with detector 17 using normal ion counting techniques. The acquired mass spectra can either be used for m/z identification or plotted as a function of ion mobility.

[0102] FIG. 17 shows the equipotential lines of a prior art device displaying a linear electric field formed by applying a voltage across a series of equally spaced rings through a resistor chain or across a tube coated with a resistive material. The linear electric field assures that all ions experience the same field independent of radial diffusion if sampled before experiencing the fringing nonlinear fields near the side wall. In the case a of stacked ring/insulating spacer assembly several factors can degrade this ideal situation, e.g. alignment becomes critical, machining errors multiply with drift cell length, resistors must be perfectly matched, and the insulating spacers eventually degrade leading to perturbations in the linear field. It is also very difficult to coat a tube evenly with a resistive material. An alternative method to produce a linear electric field is simply