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Mass-selective ion accumulation and fragmentation in a linear octopole ion trap external to a Fourier transform ion cyclotron resonance mass spectrometer

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Abstract

Electrosprayed protein ions are accumulated and mass selected in an external linear octopole trap before injection into a Fourier transform ion cyclotron resonance (FTICR) mass spectrometer. Mass selection is performed by application of superimposed rf and dc octopole electric potentials during ion accumulation. Ion trajectory stability and mass selection in the octopole field are explained qualitatively by analogy to a quadrupole mass filter. Accumulation of ions from a selected *m/z* range is demonstrated experimentally for 7 and 9.4 T electrospray ionization (ESI) FTICR mass spectrometers. Ion fragmentation in the octopole may occur under certain operating conditions. (Int J Mass Spectrom 198 (2000) 113–120) © 2000 Elsevier Science B.V.

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1. Introduction

Ion mass (or more precisely, mass-to-charge ratio, *m/z*) selection is based on the stability (or instability) of ion motion in electric and/or magnetic fields. For linear devices (i.e. the electric field varies linearly with dimension), ions of a narrow *m/z* range may be isolated (in a quadrupole ion trap) or filtered (in passing through a quadrupole ion guide). Ever since Wolfgang Paul invented the quadrupole mass filter in the early 1950s [1], its mass-selective ability has been widely known and exploited [2–6]. Operation of the quadrupole (two- or three-dimensional) is most readily understood from its so-called “stability” diagram [2,3]. For example, the boundaries of the first stability region of the diagram define the maximum combined rf and dc voltages below which ion trajectories are stable (i.e. ions are not lost from the device).

A similar analysis can be extended (in the adiabatic or “pseudopotential” approximation [7]) to higher-order multipole electric potential fields (e.g. hexapole, octopole), in the limit of zero dc potential (i.e. rf-only operating mode) [8]. A two-dimensional octopole (or a hexapole) may be used to transfer, guide, and collimate ions [9–19].

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For example, linear two-dimensional octopoles and hexapoles are commonly operated in rf-only mode (i.e. essentially nonselective in *m/z*) to accumulate and/or transfer ions from an electrospray ionization (ESI) source to a mass analyzer [20–26]. As a result, the ion trap [Paul or ion cyclotron resonance (ICR)] mass analyzers must accommodate both analyte ions and other ions, making it difficult to characterize low-abundance analytes in complex mixtures and/or in the presence of more abundant impurities or contaminants. Dynamic range is especially problematic for trapped-ion mass analyzers because there is an upper limit to the total number of ions that can be confined in such a trap without degrading the mass spectral peak shape and mass accuracy [27,28].

By analogy to a quadrupole ion guide or trap, superimposing a dc voltage on the rf voltage applied to a multipole ion guide or trap should make it possible to eliminate ions outside a selected *m/z* range before they reach the mass analyzer. That makes it possible to fill a Paul or Penning ion trap with *m/z*-selected ions only, thereby increasing dynamic range in the final mass spectrum (e.g. by accumulating/transmitting analyte ions but not impurity or contaminant ions of different *m/z*).

In a Paul or Penning trap, it is of course possible to trap ions, either batchwise or continuously, while simultaneously ejecting (optimally by stored waveform inverse Fourier transform (SWIFT) dipolar excitation [29,30]) ions of unwanted *m/z* value(s) or (in a Penning trap) by selectively axializing ions of a single *m/z* value by azimuthal quadrupolar excitation [31–34]. However, if done batchwise, then the dynamic range is still limited by the total number of ions of all *m/z* present initially, and if done continuously, then it is necessary to introduce a relatively high pressure of collision gas in the trap to ensure good trapping efficiency, and the gas must then be pumped away before detection (producing an inconveniently slow duty cycle). Finally, ultrahigh mass resolving power is generally not necessary to eliminate undesired ions, so that *external* mass selection offers an attractive option. Campbell has achieved mass selection by means of resonant ejection in a linear quadrupole trap operated in rf-only mode [35].

Here, by superimposing a dc octopolar field on the rf field during ion accumulation, we achieve experimental mass resolving power of ~10 by *m/z*-selective ion accumulation in an external linear octopole ion trap, prior to ion injection (through a separate multipole ion guide) to a Fourier transform ion cyclotron resonance (FTICR) trapped-ion cell for mass analysis. The method promises to extend FTICR dynamic range significantly, as demonstrated experimentally for bovine ubiquitin.

Finally, it is well known that ions may be induced to fragment in a two- or three-dimensional electric quadrupole [35–37], and such fragmentation is widely used to reconstruct peptide amino acid sequences and other parent ion structures [38–40]. Hofstadler and co-workers have recently reported ion fragmentation in a linear hexapole trap [26]. Here, we report ion fragmentation in a linear octopole ion trap operated at appropriately combined rf and dc electric potentials.

2. Principles

2.1. Ion stability in a two-dimensional quadrupole mass filter

We begin by reviewing the mass selectivity of an ideal two-dimensional quadrupole mass filter, constituted of four infinitely extended electrode rods whose inner-facing surfaces have hyperbolic cross section, to produce a potential with $(x^2–y^2)$ spatial dependence. The four electrodes (all running parallel to a central "symmetry" z axis) can be divided into two orthogonal pairs symmetrically displaced to positive and negative x or y positions. A positive dc voltage, $+V_{dc}$, is applied to the pair on the x axis and an equal and opposite (negative) voltage, $-V_{dc}$, is applied to the pair on the y axis. An additional rf voltage of zero-to-peak amplitude, $V_{rf}\cos(\omega t)$ is applied to one of the two electrode pairs and an opposite-phase (i.e. 180° phase difference) rf voltage, $V_{rf}\cos(\omega t + \pi) = -V_{rf}\cos(\omega t)$, is applied to the other electrode pair. Ions injected parallel to the z axis (and within the circle bounded by the interior surfaces of the rods) are subjected to a radial force from the electric field of the rods. For simplicity, we shall review the behavior of ions in the so-called first stability region [2,3].

In the x direction, the force from the dc quadrupolar potential field is directed radially inward, thereby focusing ions toward the central z axis of the quadrupole. For relatively low rf voltage (i.e. relatively low quadrupolar potential field), the focusing effect of the dc quadrupole field dominates the x motion of high m/z ions, whose trajectories are stable (i.e. remain within the volume bounded by the rods). However, the x motion of lower-m/z ions (which can respond faster to a change in electric field) will be dominated by the defocusing effect of the rf quadrupolar potential field, and those ions will execute unstable trajectories and be lost. Increasing the rf voltage increases the rf quadrupolar potential field and the force deriving from it, so that the x motion of ions of increasingly larger m/z will become unstable. Thus, the combined rf and dc voltages result in a net high-pass m/z filter for stable x motion.

Conversely, the force from the dc quadrupolar potential field in the y direction is radially outward directed, tending to destabilize the y motion of ions of higher m/z, whereas the y motion of low-m/z ions is stabilized over a certain range of rf field voltage. The quadrupole thus acts as a low-m/z pass filter for stable y motion.

Overall, the quadrupole therefore passes ions within a band of m/z values determined by ion motional stability in both x and y directions. A very important feature of the quadrupole potential is that the frequencies of ion radial (and axial, in the three-dimensional quadrupole potential) periodic motions are *independent* of ion x or y position in the volume bounded by the electrodes. The reason is that force is the negative gradient of potential, so that the force acting on an ion varies linearly with x or y. As a result, a two- or three-dimensional quadrupole can be described by a single "stability" diagram that indicates whether an ion of a given m/z value will have a stable or unstable trajectory for a specified rf voltage and dc voltage, independent of ion initial position inside the device. Moreover, that stability diagram has a sharp cusp, so that it is feasible to select ions up to m/z ~4000 to within 1 m/z unit.

2.2. Ion stability in a two-dimensional octopole mass filter

The same principles apply to a two-dimensional octopole mass filter (Fig. 1). However, because the potential now varies as $(x^4 - 6\ x^2y^2 + y^4)$, the force acting on an ion is cubic rather than linear in x and y. As a result, ions of a given m/z undergo quasiperiodic x (or y) motion whose "quasi"-frequency [8] depends on ion initial position and velocity. Because ions of a given m/z no longer have a single well-defined frequency, the motional frequencies for ions of adjacent nominal masses $(m - 1)$, m, $(m + 1)$ can overlap (depending on their initial positions and velocities). The resulting stability diagram [41] has a much smoother shape, and thus much poorer optimal m/z selectivity [41]. Finally, the octopole potential field can accelerate ions to higher kinetic energy, resulting in collision-induced dissociation. A similar effect is well known for two- and three-dimensional quadrupoles, as noted above.

3. Experimental

Experiments were carried out with homebuilt ESI FTICR mass spectrometers operating at 7 and 9.4 T, as described elsewhere [20,21,42]. Bovine ubiquitin (Sigma, St. Louis, MO) was prepared in 50% methanol:50% water (vol:vol) containing 2% acetic acid. Sample concentration was 10 μm (for 9.4 T experiments) and 1 μm (for 7 T experiments).

In the linear external octopole trap, ions are confined radially by a two-dimensional electric octopole field and axially by a dc potential well. The octopole is constructed from eight rods of circular (0.16 cm radius) rather than hyperbolic cross section. However, the resulting potential field closely approximates a true octopolar potential within the area enclosed by the rods, except for locations very close to the rods. The axial dc potential well is formed by two circular endcap electrode plates (with a 5-mm-diameter circular hole in the center to allow ions to pass through) located at the entrance and the exit of the octopole. The ion accumulation octopole length is 44 cm (9.4 T

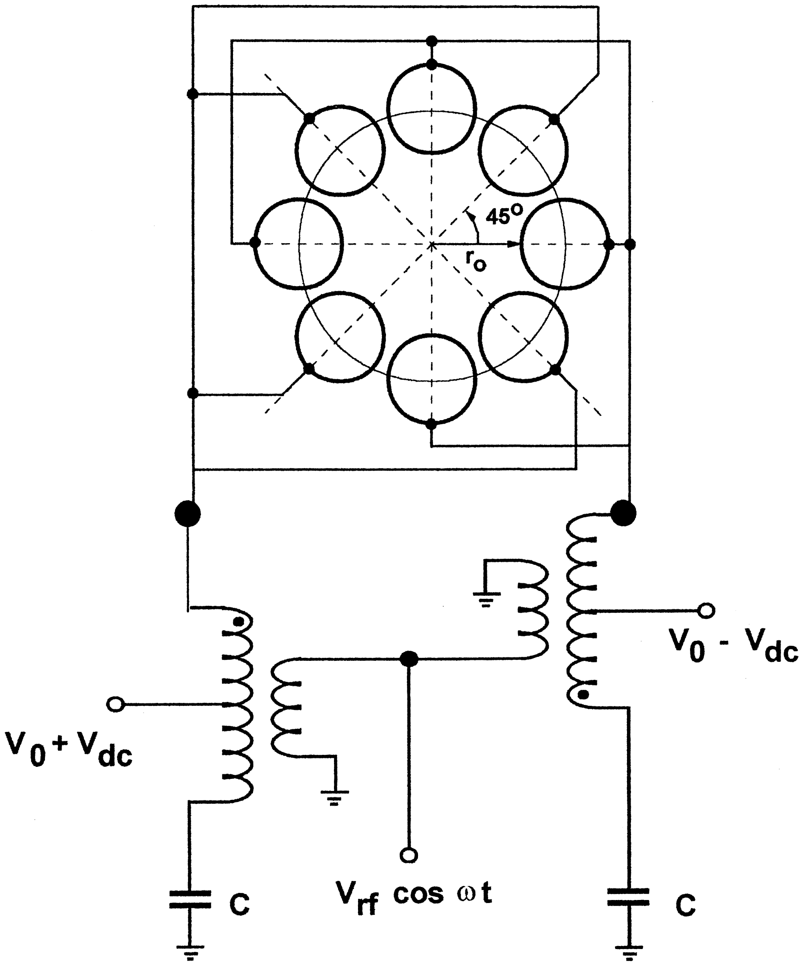

Fig. 1. Diagram of an electric octopole ion guide operated in mass-selective mode. Two interdigitated sets of four rods are evenly distributed about a circle. The voltage applied to one set of rods is $V_0 + V_{dc} + k\ V_{rf} \cos(\omega t)$, and to the other set is $V_0 - V_{dc} - k\ V_{rf} \cos(\omega t)$. The two sets therefore have opposite dc polarity and a 180° phase difference in rf voltage. V_{rf} is the zero-to-peak amplitude of the rf waveform from the power supply. V_0 is the dc offset voltage.

system) and 15 cm (7 T system). The radius, r_0, of the "inscribed" circle that just touches the inside surfaces of the rods (see Fig. 1) is 0.24 cm in both instruments. Thus, $r_0/r = 1.5$. The pressure in the octopole was typically of the order of 1 mTorr.

The arrangement for mass-selective ion external accumulation in the octopole is shown in Fig. 1, in which V_0, V_{dc}, and V_{rf} are the dc offset applied to all eight rods, the differential dc, and differential rf voltages, and ω is the rf drive (angular) frequency. The capacitor, C, is adjusted to balance the capacitance of the octopole rods to avoid rf feedback on the center taps of two identical balun transformers where the dc potential is applied. The phase difference between rf voltages applied to the two sets of four electrodes (see the small dots on the transformers in Fig. 1) is 180°. The rf voltage, V_{rf}, is generated by a function generator (model DS340, Stanford Research Systems, Sunnyvale, CA) and then amplified by a high power rf amplifier (model 2100 L, ENI, Rochester, NY). The power supply for the positive and negative dc voltages is homebuilt.

Note that in the present experiments, the rf voltage circuit does not operate in resonant mode. The rf voltage V_{rf} was measured with an oscilloscope (Tektronix TDS 460, Tektronix Inc., Wilsonville, OR) through a probe with a capacitance of ~20 pF. The measured rf voltage V_{rf} is thus ~10–15% lower than the actual value because the capacitance of the octopole itself is ~170 pF (9.4 T instrument) or ~120 pF (7 T instrument) through one set of rods to ground.

Electrosprayed ions accumulate in the external octopole trap, and are then pulsed toward the ICR cell through an ion guide (an rf-only octopole for the 9.4 T system or an rf-only hexapole for the 7 T system), by application of suitable dc voltages to the octopole rods and exit endcap. Once trapped in the ICR cell, ions are excited by standard chirp excitation with a sweep rate of 150 Hz/μs from *m/z* 3000 to 300 and an amplitude of 125 $V_{p\text{-}p}$. The ion signal is detected by broadband detection with an analog-to-digital conversion rate of 1 MHz and 512 K data points. Time-domain data are subjected to one zero-fill and Hanning apodization prior to fast Fourier transformation and magnitude calculation.

4. Results and discussion

Fig. 2 (bottom) is a broadband 9.4 T FTICR mass spectrum of electrosprayed bovine ubiquitin, obtained by operating the external octopole ion trap in an rf-only (i.e. essentially mass unselective) mode, so that all charge states are detected. The upper panel of Fig. 2 shows mass-selective accumulation in the octopole of the 9+ charge state of ubiquitin, achieved by empirical adjustment of dc voltage (V_{dc}) applied to the octopole rods. The same vertical scale is reported in all of the succeeding figures. The 9+ charge state is clearly isolated without contamination from any of the other charge states.

Fig. 3 shows similar accumulation and isolation of (primarily) the 12+ charge state of electrosprayed bovine ubiquitin in the external octopole trap of a 7 T FTICR mass spectrometer. The mass spectrum obtained with rf-only external octopole operation (Fig. 3, bottom) shows several ubiquitin charge states, whereas the application of an additional dc voltage to the octopole rods (Fig. 3, top) selects the 12+ and 13+ charge states.

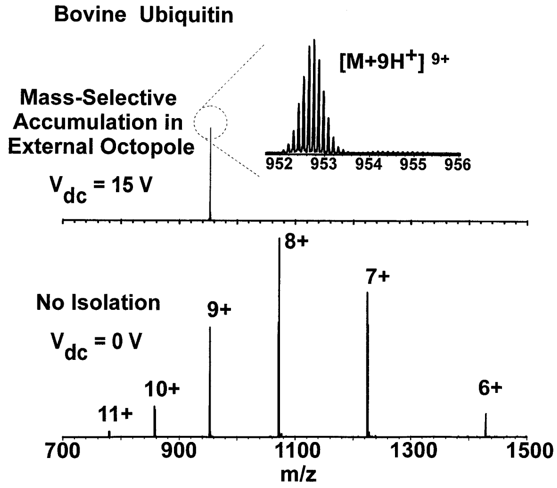

Fig. 2. External accumulation and *m/z* selection of electrosprayed bovine ubiquitin charge states, observed by 9.4 T FTICR MS. Top: external octopole ion trap operating conditions: $\omega/2\pi = 1.5$ MHz, $V_{rf} = 142\ V_{0-p}$, $V_{dc} = 15$ V. Bottom: rf-only octopole potential field ($V_{dc} = 0$ V).

Figs. 2 and 3 demonstrate that mass-selective external ion accumulation may be achieved by simul-

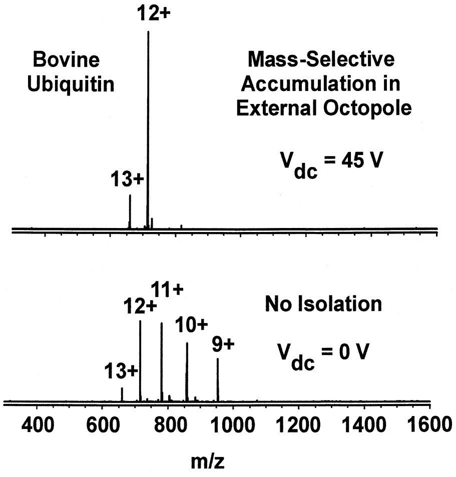

Fig. 3. External accumulation and *m/z* selection of electrosprayed bovine ubiquitin charge states, observed by 7.0 T FTICR MS. External octopole ion trap operating conditions: $\omega/2\pi = 1.2$ MHz, $V_{rf} = 262\ V_{0-p}$. Top: $V_{dc} = 45$ V. Bottom: rf-only octopole potential field ($V_{dc} = 0$ V).

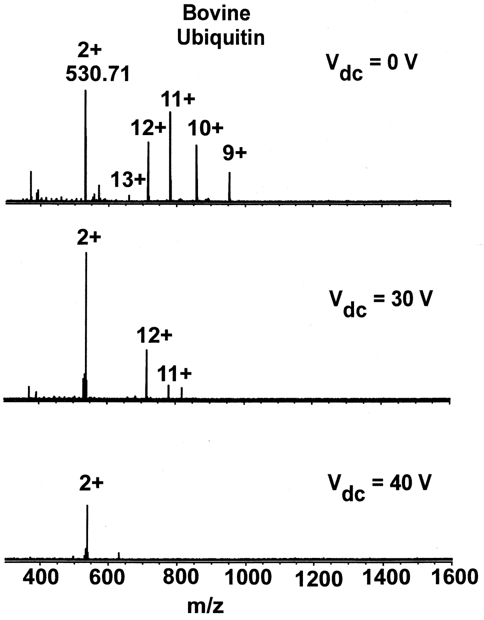

Fig. 4. External accumulation and *m/z* selection of electrosprayed bovine ubiquitin and impurity ions, observed by 7.0 T FTICR MS. External octopole ion trap operating conditions: $\omega/2\pi = 1.5$ MHz, $V_{rf} = 180\ V_{0-p}$. Top: $V_{dc} = 0$ V (rf-only mode). Middle: $V_{dc} = 30$ V. Bottom: $V_{dc} = 40$ V.

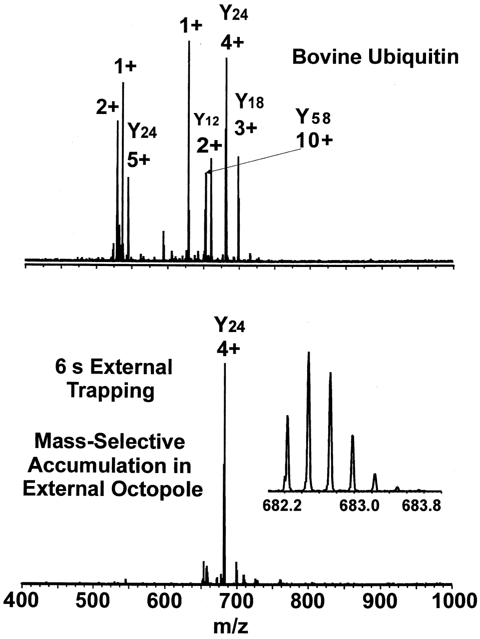

Fig. 5. External accumulation and *m/z* selection of electrosprayed bovine ubiquitin and fragment ions, observed by 7.0 T FTICR MS. Top: external octopole, $\omega/2\pi = 1.5$ MHz, $V_{rf} = 180\ V_{0-p}$, $V_{dc} = 25$ V, trapping delay period = 6 s. Bottom: external octopole, $\omega/2\pi = 1.2$ MHz, $V_{rf} = 164\ V_{0-p}$, $V_{dc} = 28$ V, ion accumulation period = 6 s.

taneous application of appropriate dc and rf voltages to an external octopole ion trap. Ions whose *m/z* values fall within the *m/z* selection window execute stable trajectories in the octopole, whereas ions whose *m/z* values lie outside the selection window have unstable trajectories and are lost. A major advantage of external mass selection is that the ICR trapped-ion cell may be filled with the same number of ions of fewer *m/z* values, for significantly increased signal-to-noise (S/N) ratio for ions whose initial relative abundance is low—e.g. compare the S/N for ubiquitin 12+ and 13+ charge states in Fig. 3 (top) versus (bottom). Thus, external ion selection can extend significantly the dynamic range of ESI FTICR MS for analysis of complex mixtures.

Fig. 4 illustrates mass selection of ions from a mixture (in this case, ubiquitin electrosprayed at low concentration, so that impurities become observable). The full *m/z* range is observed by external accumulation of ions in rf-only octopole operation (Fig. 4, top). As the octopole dc voltage increases (Fig. 4, middle and bottom), the selected *m/z* range narrows. The data also demonstrate that some ions within the selected *m/z* range are lost as the octopole dc voltage increases (compare Fig. 4, middle and bottom). Moreover, mass selectivity for an octopole is not as narrow as for a quadrupole ion trap, because the stability diagram is flatter at the top (rather than coming to a sharp corner, as in a quadrupole ion trap) [8,41]. In agreement with theoretical simulations [8,41], we are unable to achieve unit mass selectivity for external octopole ion accumulation. Nevertheless, the octopole has other advantages, notably lower rf operating voltage (about four times greater pseudopotential for a given applied voltage [8]), and a wider *m/z* range.

Another characteristic of external octopole ion accumulation is that ions may fragment as the mass window is narrowed and/or rf frequency is increased and/or residence time in the trap is increased. For example, Fig. 5 shows multiple fragment ions from electrosprayed ubiquitin (and impurities). Note that mass selection is still observed because only fragments whose *m/z* values fall within the octopole selection range are accumulated and subsequently detected by FTICR MS. The effect is especially apparent in Fig. 5 (bottom), obtained under conditions producing a narrower octopole ion stability *m/z* range. Nonselective fragmentation has been observed previously in a linear hexapole [26]. Finally, Voyksner and Lee recently described the use of an rf-only octopole ion guide for accumulation and high-pass mass filtering of ions prior to introduction to a quadrupole ion trap mass analyzer [25]. However, their method limits only the upper mass limit, whereas the present method (in which both rf and dc voltages are varied) defines both ends of a specified *m/z* range.

5. Conclusion

Mass-selective (actually, *m/z* selective) accumulation and fragmentation of electrosprayed ions in an external linear octopole trap have been characterized by subsequent FTICR mass analysis. Mass resolving power in the external octopole is found to be limited to ~10. Significant ion loss and ion fragmentation preclude narrower *m/z*-range selection. The experiments show that more fragment ions are generated at higher rf frequency (e.g. 1.5 MHz), higher dc operating voltage, and longer external trapping period. Fragmentation cannot be reduced by lowering the rf frequency, because ion motion then becomes unstable. Finally, in the present experiments, our ability to vary the position of the *m/z*-selection window is limited by an rf voltage upper limit in our electronics. In the future, we shall introduce resonant circuitry so as to be able to vary the *m/z*-selection window by simultaneously changing the rf and dc voltages.

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