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Studies into the selective accumulation of multiply charged protein ions in a quadrupole ion trap mass spectrometer

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Abstract

In seeking to improve the limit of detection of an electrospray ionization/quadrupole ion trap mass spectrometer (ESI/ITMS) for the analysis of multiply charged protein ions, studies related to the selective accumulation of these ions during ion injection have been undertaken. This was achieved by the interfacing of an Odyssey data system and the associated electronics used for arbitrary waveform generation from a Fourier transform mass spectrometer (FTMS) (ThermoFinnigan, Bremen, Germany) to an LCQ^{TM} 'classic' quadrupole ion trap mass spectrometer (ThermoFinnigan, San Jose, CA). This allows the application of user defined stored waveform inverse Fourier transform (SWIFT) waveforms. These studies examined the efficiency of ejection and isolation at different q_z values for a particular charge state from the distribution of ions usually observed with the electrospray ionization of proteins, and the variation in the intensity of a particular ion as a function of the accumulation time. In addition, this selective accumulation technique allowed for an order of magnitude improvement in the detection limit of this instrument, with the resulting reduction in space charge producing a five-fold increase in spectral resolution (FWHM) under the conditions studied.

Keywords: Quadrupole ion trap mass spectrometry; SWIFT; Proteins; Selective accumulation

1. Introduction

The quadrupole ion trap mass spectrometer (ITMS) [1] has been developed into one of the most versatile mass spectrometers available since first being disclosed in 1956 [2].

Ion trapping instruments, however suffer from space charge effects [3–7]. These effects cause ions to be ejected later than would be expected with a decrease in the resolution of the peak. The space charge effects experienced by each ion are the result of several contributory factors: (i) the total number of ions in the ion trap, (ii) the total number of ions of the same *m*/*z* value and (iii) the abundance and mass difference of neighbouring ions [7]. Therefore, there is an optimum number of ions that can be trapped that provides maximum ion intensities before space charge effects degrade instrument performance. Consequently, it would be preferable to limit the number of ions being stored within the ion trap, only to the ones of interest.

There are two periods in the ion trap timing sequence during which ions may be isolated, either after ion injection/production and before spectral

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acquisition, as is the standard method, or during ion injection/production. The two major advantages of performing ion isolation during the ion injection period are that unwanted ions such as matrix ions do not fill the ion trap, and more of the ions of interest can be accumulated within the ion trap.

There have been several studies describing the selective accumulation of ions during ion injection/production within a quadrupole ion trap. These involve the application of appropriate waveforms to the end-cap electrodes to eject all but the ions of interest from the ion trap during ion production or ion injection. Mcluckey et al. [8] applied a large voltage ($30\,V_{p-p}$) fixed frequency pulse during ion injection to eject matrix ions produced during ionization with an ASGDI source. There have been several broad-band resonant ejection techniques applied to ion traps. These include the stored waveform inverse Fourier transform (SWIFT) technique [9–16], filtered noise fields (FNF) [17–19] and field modulated constructed waveforms [20,21]. The SWIFT technique was first developed for ion cyclotron resonance mass spectrometers [22,23]. It involves taking a desired excitation spectrum with the corresponding phase function and applying an inverse Fourier transform to obtain the time domain waveform needed to cause broad-band excitation of trapped ions. A number of groups have subsequently applied this technique to quadrupole ion trap mass spectrometers. Cooks and Soni [12] observed up to a 1000-fold increase in signal to noise for the peptide substance *P* while using SWIFT waveforms for the selective accumulation of ions produced by caesium ion bombardment of a peptide. Mann and coworkers [24] used SWIFT waveforms during ion injection to selectively accumulate small singly and doubly charged peptide ions of low intensity, and to improve the dynamic range of the ion trap.

The FNF technique consists of a basic digitally synthesised waveform with evenly spaced (typically every 250, 500 or 1000 Hz) frequency components spanning the secular frequency spectrum of the entire ion trap *m*/*z* range. Frequency components can then be added or removed to eject or retain any desired ion within the ion trap. This technique has been successfully utilised to achieve the selective accumulation of single or multiple mass range windows [17]. Field modulated constructed waveforms reduce the density of the frequency components by varying the RF voltage on the ring electrode during ion formation or injection. This allows any particular resonant ejection voltages applied to the end-cap electrodes to promote ejection of ions of different *m*/*z* [20,21]. All the above studies were carried out with low molecular weight chemicals or small singly and doubly charged peptides.

The application of these techniques to highly charged, high molecular weight protein ions has yet to be examined. Compared with singly or doubly charged ions, the presence of several charges on the multiply charged ions arising from the electrospray ionization of proteins will intensify the phenomenon of space charge effects these ions will experience. Also these multiply charged protein ions are sufficiently fragile that they are susceptible to fragmentation from off-resonance excitation during the application of ejection waveforms to remove unwanted ions from the trap.

The RF voltage on the ring electrode is usually referred to in terms of the Mathieu parameter q_z which is given by the following expression

$$\frac{8eV_{(0\text{-p})}}{m\left(r_0^2 + 2z_0^2\right)\Omega^2} \tag{1}$$

where e is the charge on the ion, $V_{(0\text{-p})}$ is the maximum RF potential applied between the ring and the end-caps, m is the mass of the ion, r_0 is the radius of the ring electrode $2z_0$ is the closest distance between the end-caps and Ω is the angular frequency of the RF drive potential. Ion isolation is usually performed at higher q_z values (0.7–0.8) than ion injection (0.05–0.2). Hence, before studying ion accumulation during ion injection into the ion trap a set of experiments were performed to establish the experimental conditions necessary to isolate and eject multiply charged ions without inducing fragmentation at the low q_z values which have been found to be optimal for ion injection [25].

Once the criteria for selective accumulation during ion injection had been established a set of experiments examining ion intensity versus accumulation time and the potential for improvement in detection limit and spectral resolution were performed. All of these experiments necessitated the application of specific waveforms to the end-cap electrodes of an LCQ™ 'classic' ion trap mass spectrometer. To achieve this we used an Odyssey data system and the associated electronics used for arbitrary waveform generation taken from a Fourier transform mass spectrometer (FTMS). Vachet and McElvany [26] also interfaced a SWIFT generator to the LCQ™ 'classic' in order to apply externally generated waveforms during the ion isolation and excitation periods in order to perform complex ion manipulations with small singly charged peptides and chemicals. The waveform generator in our studies was interfaced after the auxiliary amplifier board in the LCQ™ as opposed to before it, as in Vachet and McElvany's paper, as this allowed the user control over the amplitude of the waveform being applied. The auxiliary amplifier board sets the amplitude of the waveform to a value determined by the scan parameters used.

In this paper work on the selective accumulation of multiply charged protein ions via the application of externally generated waveforms applied during ion injection are presented. It will be demonstrated that by this technique it is possible to improve both the detection limit of the instrument and the spectral resolution (via the reduction of space charge effects).

2. Experimental

2.1. Instrumentation

All experiments were performed on an LCQ™ 'classic' ion trap mass spectrometer (ThermoFinnigan, San Jose, CA) equipped with a standard on-axis electrospray source. Customised waveforms were generated on an Odyssey data system and the associated arbitrary waveform generator electronics from an FTMS (ThermoFinnigan, Bremen, Germany) and replaced the waveforms produced by the LCQ™ on-board wavecard (Fig. 1). The external waveforms, once generated were stored on the Odyssey system until they were automatically triggered by a transistor-transistor logic (TTL) signal produced on pin TP15-3_Sync TP of the main power board of the LCQ™ that coincides with the start of the analytical scan (J.C. Schwartz, personal communication, 1996). This TTL signal from pin TP15-3_Sync TP was input to pin 5 of the Odyssey data system I/O array. As all the waveforms normally produced by the LCQ™ were disconnected, the RF waveform at 348 kHz used for axial modulation was also supplied by the

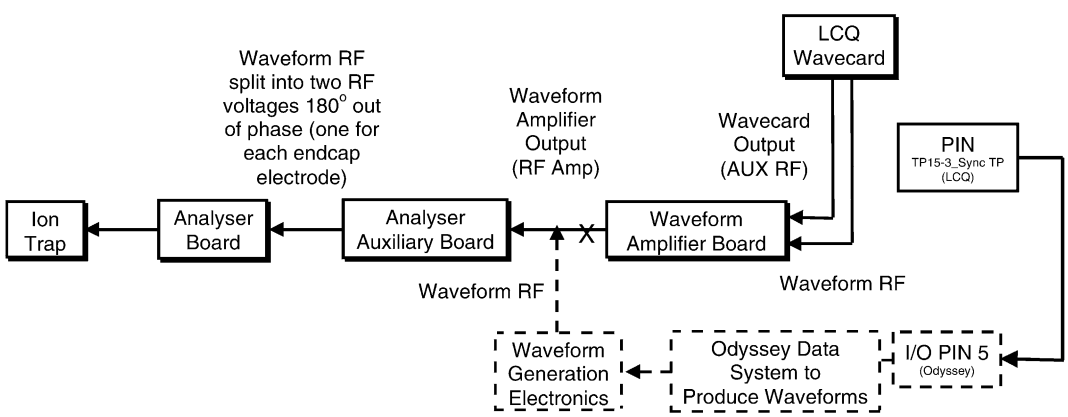

Fig. 1. Schematic describing the interfacing of the Odyssey data system with associated electronics to the LCQ™ 'Classic'.

Odyssey data system. The axial modulation waveform produced on the Odyssey data system differed from that generated by the LCQ™ as the amplitude of the waveform applied was set at a constant value during the acquisition phase and was not ramped as is the standard method.

In the routine operation [27] of the LCQ™ 'classic' in full scan mode, up to four steps in the RF voltage are used during ion injection to allow the most efficient injection of ions across the entire mass range. In order to apply only one type of SWIFT waveform, the SIM or MS/MS modes of the LCQ™ 'classic' were employed as these use a constant RF voltage on the ring electrode during ion injection.

The electrospray needle on the LCQ™ was set to 4 kV, the heated capillary at 250 °C and the flow rates of the nebulising and auxiliary gases to 60 and 10 arbitrary units, respectively. The lensing system was then optimised for the maximum transfer of the principal ion of interest from the electrospray source into the ion trap.

2.2. Materials

Ubiquitin from bovine red blood cells and enolase from bakers yeast were purchased from Sigma (Poole, Dorset, UK) and used without further purification. All samples were made up to the concentrations indicated in 1:1 (v/v) methanol:water with 0.1% formic acid.

3. Results and discussion

The first two sections describing experiments performed during the ion excitation phase were designed to determine the efficiency of ejection and isolation of a particular charge state from the distribution of multiply charged ions produced by electrospray ionization of proteins. The optimal q_z value for ion injection of a particular ion is very dependent on its velocity on entering the ion trap [28], and has been observed experimentally to be in the range $q_z = 0.05$–0.2 [25]. It is important to note that using a low q_z value such as those typically associated with ion injection will have several consequences for ion isolation and ejection. Ions will be contained within a shallower potential well [4,29], and therefore may be ejected more readily. There will be a reduction in the spread of the frequencies between ions of similar m/z thus ions are more likely to be excited by an off-resonance excitation. The following experiments

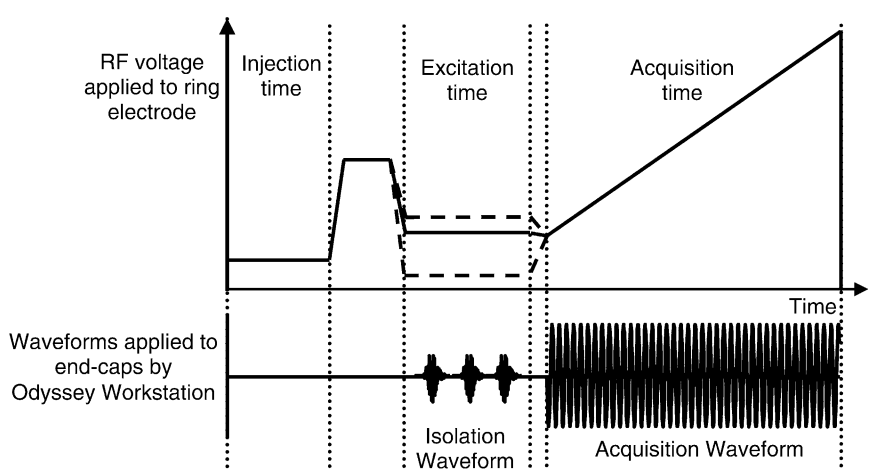

Fig. 2. Schematic describing the MS/MS scan function modified for ejection and isolation at different RF voltages during the excitation phase.

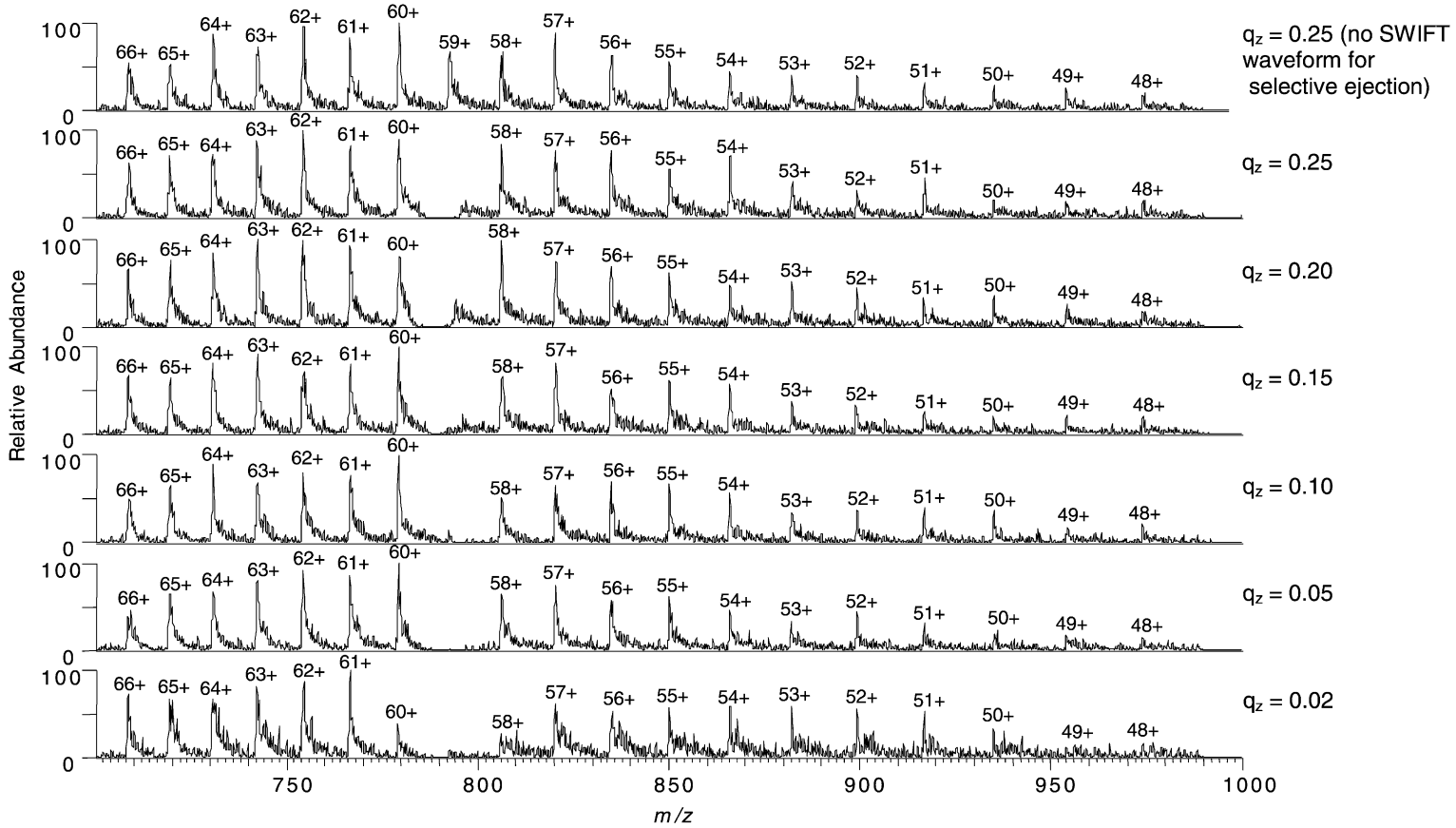

Fig. 3. Selective ejection of the $[M + 59H]^{59+}$ ion of enolase at different q_z values.

were performed by using the standard MS/MS RF voltages on the ring electrode, and by applying external customised isolation waveforms to the end-cap electrodes. The experimental sequence used is shown in Fig. 2.

3.1. The ejection of a specific ion charge state at different q_z values

The yeast protein enolase (MW 46,670.97 Da) was used to study the ease of ejection of a specific ion

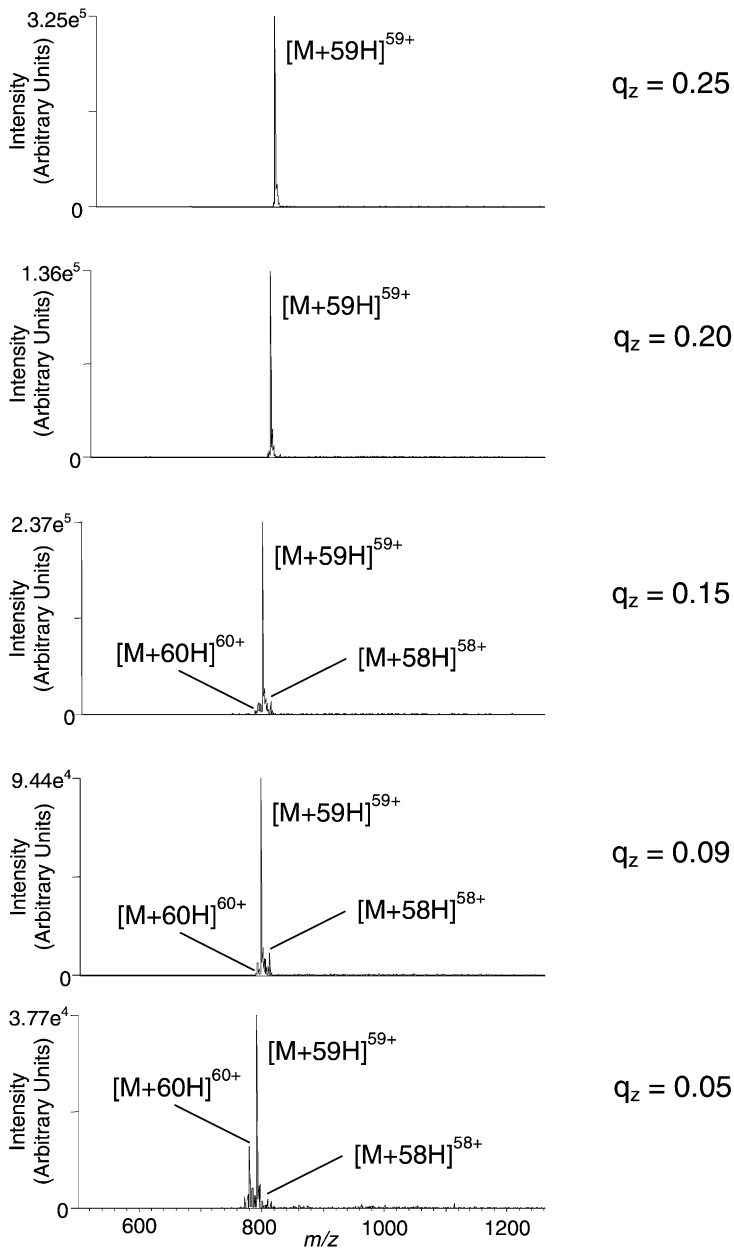

Fig. 4. Selective accumulation of the $[M + 59H]^{59+}$ ion of enolase at different q_z values.

without the ejection of the adjacent charge states. For a protein of molecular weight 46,670 Da the difference in m/z ratio between the $[M + 59H]^{59+}$ ion and the adjacent charge states ($[M + 58H]^{58+}$ and $[M + 60H]^{60+}$) is only 13 m/z units. The experiment was performed by direct infusion of a solution of enolase (50 fmol/μl) into the instrument. The q_z value at which the $[M + 59H]^{59+}$ ion was ejected was varied. For each value of q_z the frequency and amplitude of the resonance ejection pulse was tuned for optimal ejection of the $[M+59H]^{59+}$ ion without loss of the adjacent $[M+58H]^{58+}$ or $[M+60H]^{60+}$ ions. The results of this experiment are shown in Fig. 3. These data demonstrate that the $[M+59H]^{59+}$ ion can be ejected without significant loss of the adjacent charge states down to $q_z = 0.02$, at which point some ejection of the adjacent charge states is observed.

3.2. The selective accumulation of a specific ion charge state at different q_z values

The selective accumulation of a single charge state at low q_z values is however more difficult to achieve than its ejection. This is because the selected ion experiences excitation from both the higher frequency waveform to eject low m/z ions and the lower frequency waveform to eject the higher m/z ions. This difficulty with ion isolation is demonstrated in Fig. 4 for the isolation of the $[M+59H]^{59+}$ ion of enolase at a series of q_z values. For each value of q_z the frequency, width and amplitude of the notch in the SWIFT waveforms were tuned to allow for the maximum amount of the $[M+59H]^{59+}$ ion to be accumulated with the least amount of the adjacent charge states. The isolation of the $[M + 59H]^{59+}$ ion at q_z values 0.25 and 0.2 was easily performed, without loss in ion intensity or observation of the adjacent charge states. As discussed in Section 3 decreasing the q_z has two effects; the reduction of the depth of the potential well and a reduction in the spread of the frequencies between ions of similar m/z. Both result in increased off-resonance ejection of ions. Thus, it was not unexpected that, when lower values of q_z (0.15 and below) were used it was necessary to increase the width of the isolation window in order to avoid loss of the charge state of interest from off-resonance ejection. By widening the isolation window, however, some of the neighbouring charge states were observed in the resulting spectrum.

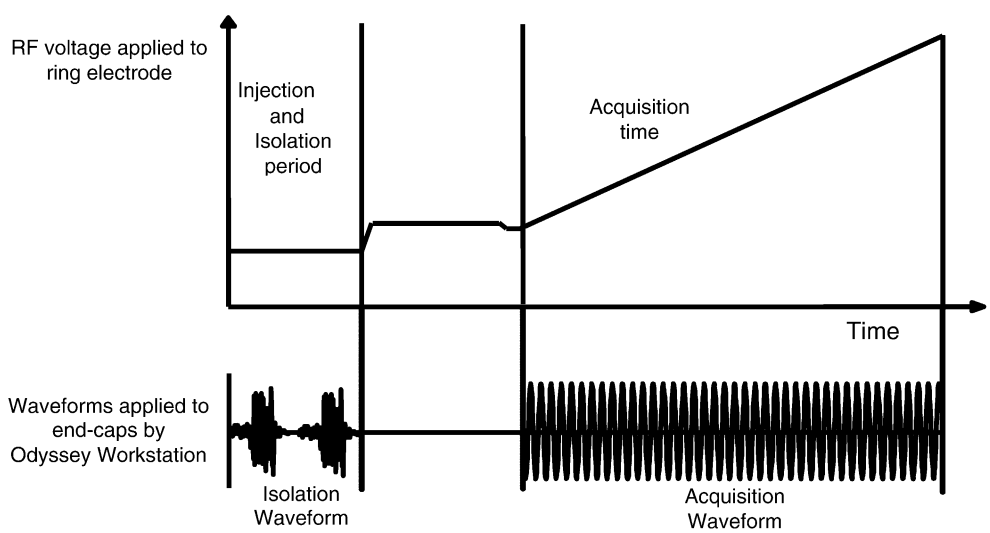

Fig. 5. Schematic describing the SIM scan function modified for selective injection using SWIFT waveforms generated by the Odyssey data system.

3.3. Selective accumulation of a multiply charged protein ion during ion injection

Having demonstrated that it is possible to isolate and eject multiply charged protein ions at the low q_z values normally associated with ion injection, SWIFT waveforms were designed to allow for the selective accumulation of a particular ion during the ion injection phase. During the ion injection phase ions are slightly more energetic, they have larger orbits and hence slightly different frequencies [30]. These experiments were therefore performed with slightly wider isolation windows than in the previous experiments to take this into account. These experiments were carried out using the conventional SIM sequence as described in Fig. 5.

In order to determine if the application of SWIFT waveforms during ion injection resulted in an improvement in the detection limit of the instrument, the q_z value for optimum ion injection as opposed to that which allows for optimal ion selectivity was chosen. Experiments were designed such that the ions produced from 5 μl loops of the protein of interest at a specified concentration were injected into the ion trap for a defined injection time, both with and without the application of SWIFT isolation waveforms. Maximum peak height was then plotted against injection time. Peak height rather than peak area was chosen because

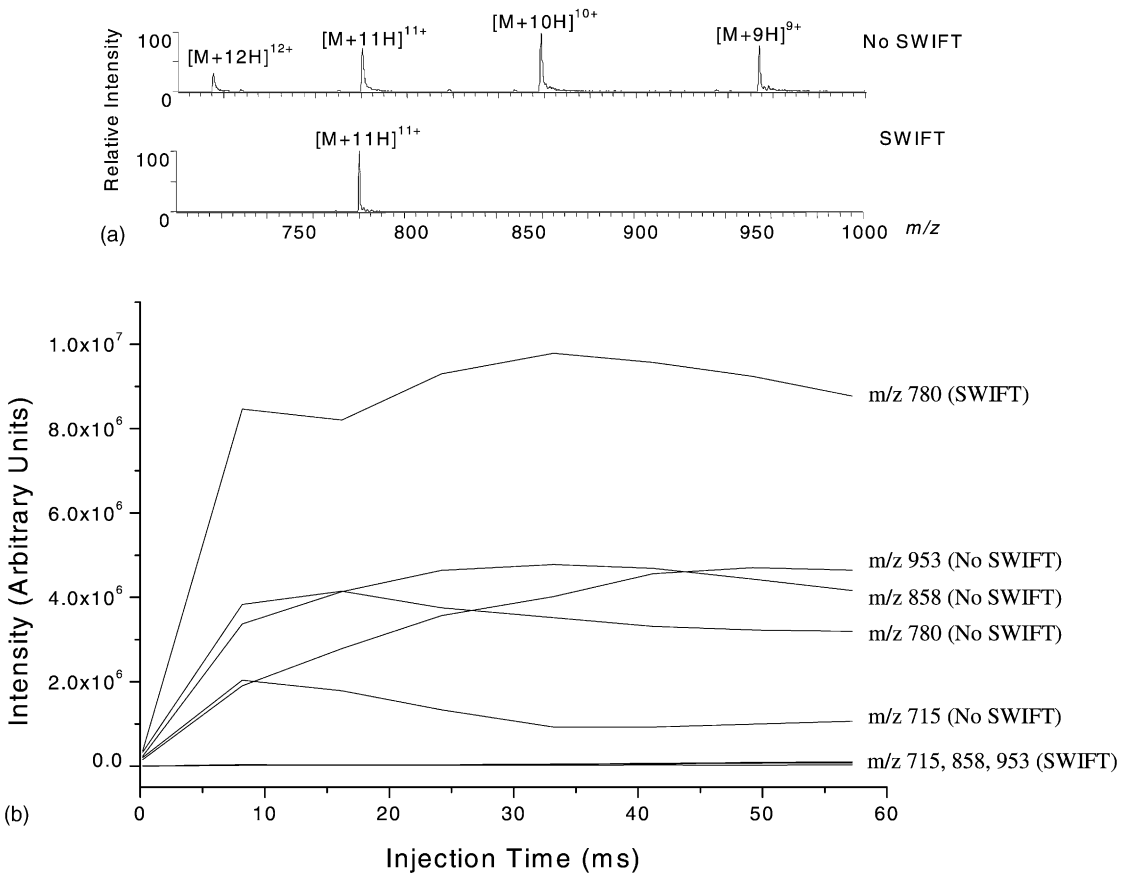

Fig. 6. (a) Electrospray mass spectrum of the $[M+9H]^{9+}$ to $[M+12H]^{12+}$ charge states of ubiquitin acquired with and without waveforms to selectively accumulate the $[M+11H]^{11+}$ ion, (b) graph showing the variation in the ion intensity with increasing ion injection time for the $[M+9H]^{9+}$ to $[M+12H]^{12+}$ charge states of ubiquitin acquired with and without waveforms to selectively accumulate the $[M+11H]^{11+}$ ion.

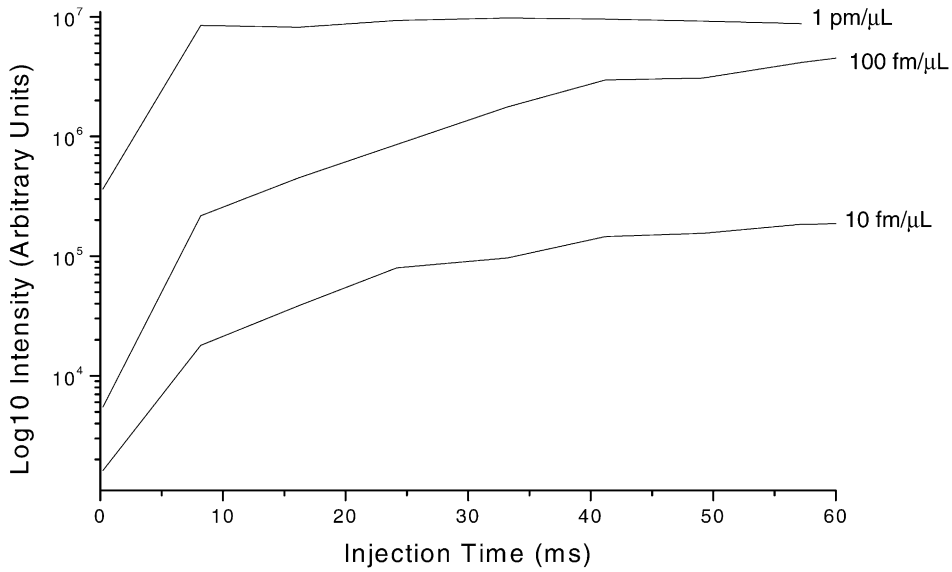

Fig. 7. Graph showing the variation in the ion intensity of the $[M + 11H]^{11+}$ ion of ubiquitin with increasing ion injection time.

the parameter of interest is limit of detection. The limit of detection is defined in terms of the least amount of sample that gives a signal that is intense enough to be distinguished from the background noise, therefore peak height not area is the important factor. This was carried out for a 50 fmol/μl solution of the protein ubiquitin and the results are presented in Fig. 6. With no ion selection, there is a linear increase in the intensity of the different charge states with injection time, until a maximum is reached after which the intensity remains constant. This maximum represents the point at which the trap has reached its spectral space charge limit [31], (i.e., the maximum number of ions that can be stored before the resolution of the mass spectrum degrades passed a specified point, defined in this case as the point at which peak intensity ceases to increase with the number of ions stored). In the case where the $[M+11H]^{11+}$ ion of ubiquitin (*m*/*z* 780) is selectively accumulated in the absence of all other ions, the maximum intensity of this ion is also observed to increase with ion injection time. It also accumulates at a faster rate and to a higher maximum intensity, than for the case where it is not selectively accumulated. It is interesting to note that, although it might be expected that the intensity of the selected ion (*m*/*z* 780) would be equivalent to the sum of the intensities of all the other ions observed in the non selective spectrum, this was not the case. This suggests that there is a limit on the number of ions of a particular *m*/*z* contributing to the signal intensity (due to space charge effects). Our results also show that the injection time at which the ion intensity reaches a maximum is dependent on the concentration of the protein sample. Fig. 7 presents graphs of intensity of the $[M+11H]^{11+}$ ion of ubiquitin as a function of injection time for different sample concentrations. The initial slope of the graph, up to the point where the ion trap has reached its spectral space charge limit, is concentration dependent and relates to the rate of ion production in the source and ion transfer into the trap. These results have also been reproduced with enolase (data not shown).

3.4. Improvement in spectral resolution through the selective accumulation of protein ions during ion injection

Another advantage of the selective accumulation of ions during ion injection should be an improvement

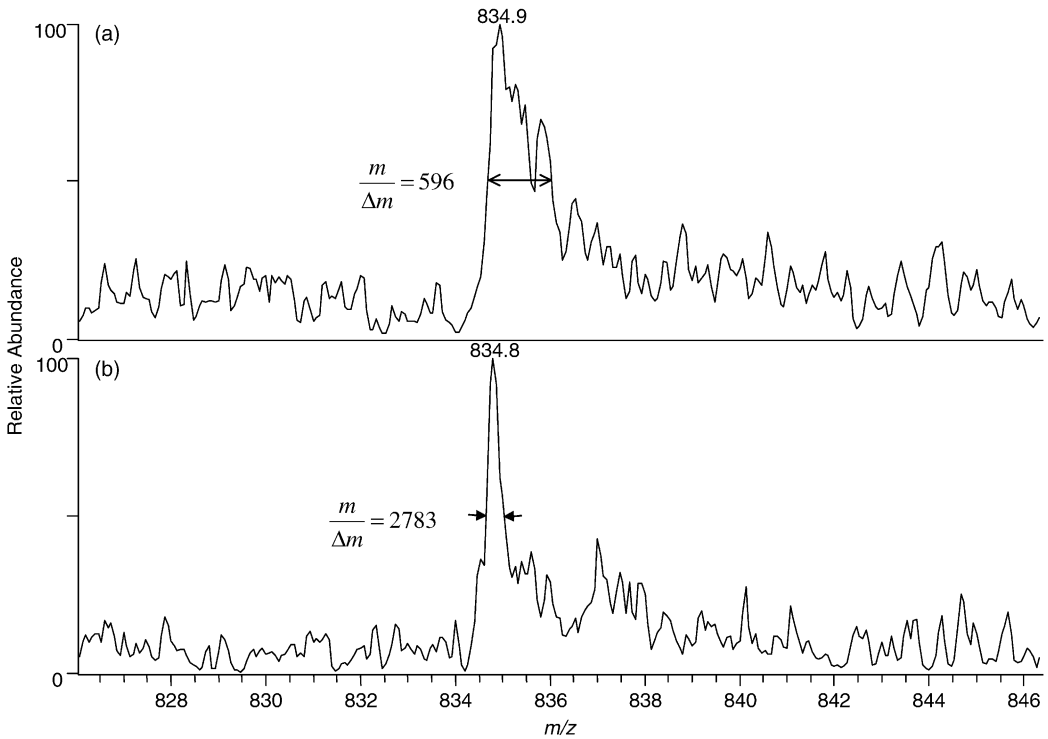

Fig. 8. Electrospray mass spectrum of the $[M + 56H]^{56+}$ ion of enolase obtained at an accumulation time of 8.5 ms (a) without selective accumulation waveforms, (b) with selective accumulation waveforms.

in spectral resolution. This was demonstrated by comparing the spectral resolution of a set of five adjacent peaks of enolase accumulated with and without the SWIFT waveforms for selective accumulation. A five-fold improvement in spectral resolution (FWHM) was observed for each peak in the set. Fig. 8 shows this increase for one of the five ions selected. This increase in spectral resolution may be explained by the lower total number of ions and the reduced number of charge states allowed into the trap in the selective accumulation process. This results in reduced space charge effects and hence an improvement in the spectral resolution of the selected ions.

3.5. Lower limit of detection through selective accumulation of a protein ion during ion injection

In the previous sections it has been shown that by using SWIFT waveforms for the selective accumulation of protein ions during ion injection it is possible to store more of the ion(s) of interest in the ion trap. This would suggest that the detection limit for the selected ion(s) should decrease accordingly. This was demonstrated in the following experiment where 5 μl loops of ubiquitin were injected at concentrations ranging from 1 to 100 fmol/μl for a set accumulation time. This was performed both with and without the application of SWIFT waveforms designed to accumulate selectively the $[M + 11H]^{11+}$ ion. The results of this experiment are shown in Fig. 9, and demonstrate an order of magnitude improvement in the limit of detection toward the $[M+11H]^{11+}$ ion of ubiquitin.

It is interesting to note that the chemical noise in the spectrum drops when the selective accumulation waveforms are applied. Experiments performed with the selective accumulation of blanks (data not shown) have shown that this may be explained as follows. The notch in the SWIFT waveform is carefully tuned to

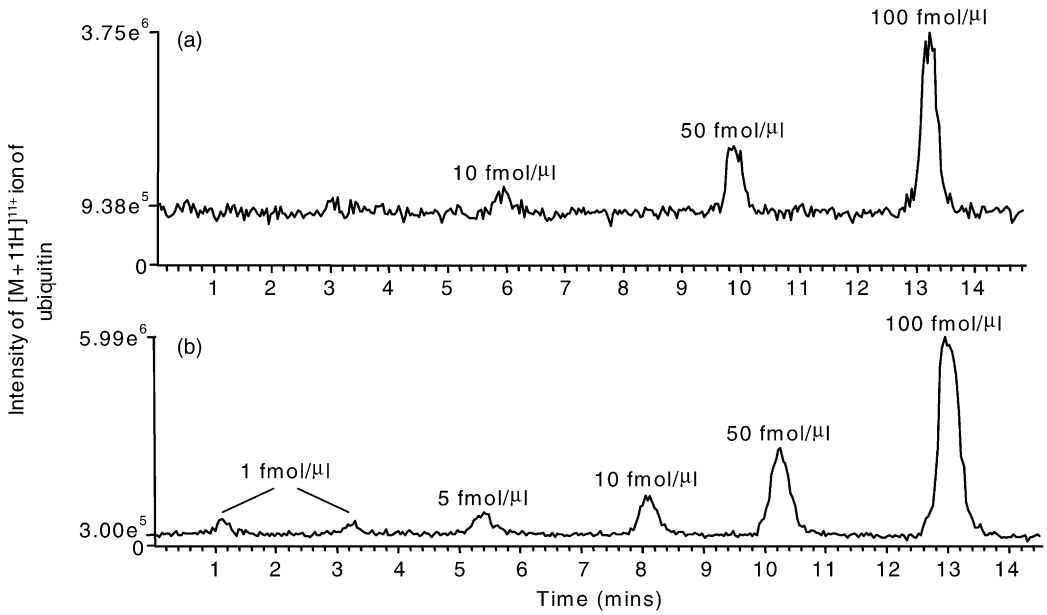

Fig. 9. Reconstructed ion chromatogram of the $[M + 11H]^{11+}$ ion of ubiquitin at the concentrations indicated, (a) without selective accumulation waveforms, (b) with selective accumulation waveforms.

allow the selective accumulation of the $[M + 11H]^{11+}$ ubiquitin ion. In order to ensure that none of the ion of interest is lost, the notch is set sufficiently wide to avoid off-resonance excitation of this ion (which is a problem at the low q_z values associated with ion injection as discussed in Section 3). Chemical noise within this notch is also selectively accumulated, but it is not accumulated to the same degree as the ion of interest. This is because the chemical noise is more prone to off-resonance excitation since these ions are not centred in the notch as is the ion of interest. Therefore, many of these ions are ejected. Any chemical noise exactly co-incident with the ion of interest will be selectively accumulated just as the chosen ion, but will be masked by this ion.

4. Conclusions

The LCQ™ 'classic' ion trap mass spectrometer was modified by the interfacing of an Odyssey data system and the associated arbitrary waveform generator electronics after the auxiliary amplifier board to allow the application of SWIFT waveforms to the end-cap electrodes. The interfacing of the waveform generator after the auxiliary amplifier allowed tuning of both the frequency and the amplitude of the waveforms applied, thus, the waveforms for selective ejection could be optimised for the ions of interest.

When selectively ejecting or accumulating a particular ion from the charge state distribution of a protein as large as enolase (46 kDa), a compromise must be made between the optimal q_z value for ion injection and the resolution of isolation. Selective ejection of the $[M + 59H]^{59+}$ ion of enolase during the excitation phase was achieved without significant loss of the adjacent charge states down to q_z values of 0.02.

The selective accumulation of a particular charge state during ion injection has two advantageous consequences. Firstly, a greater number of the selected ions can be trapped and hence, the detection limit of the instrument towards that ion is improved. An order of magnitude improvement in the limit of detection of the mass spectrometer has been demonstrated for

the $[M + 11H]^{11+}$ ion of ubiquitin. Secondly, an improvement in spectral resolution is obtained. This is due to a reduction in space charge effects from a reduction in the number of ions present in an ion trap. A five-fold improvement in spectral resolution (FWHM) was shown for the selective accumulation of the ions studied.

The studies reported here are currently being extended to the higher q_z values that are normally associated with ion isolation to gain an improvement in the resolution of isolation. This would also examine selective accumulation during the ion injection phase to allow for an ion or series of ions to be selected from a complex background. This would offer improvements in detection limit, spectral resolution and in the effective dynamic range of the instrument.

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