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RESEARCH ARTICLE

Ion Isolation in a Linear Ion Trap Using Dual Resonance Frequencies

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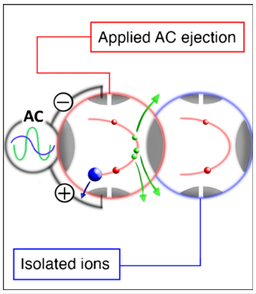

Abstract. Ion isolation in a linear ion trap is demonstrated using dual resonance frequencies, which are applied simultaneously. One frequency is used to eject ions of a broad *m/z* range higher in *m/z* than the target ion, and the second frequency is set to eject a range of ions lower in *m/z*. The combination of the two thus results in ion isolation. Despite the simplicity of the method, even ions of low intensity may be isolated since signal attenuation is less than an order of magnitude in most cases. The performance of dual frequency isolation is demonstrated by isolating individual isotopes of brominated compounds.

Keywords: Linear ion trap, Ion isolation, Tandem mass spectrometry

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Introduction

This paper is the first in a trio in which new ion trap resonance methods are demonstrated. The entire spectrum of mass analysis is explored from ion isolation to ion excitation and finally to resonance ejection. Efficient broadband ion fragmentation is demonstrated using multigenerational collision-induced dissociation [1], and successive resonances for ion ejection for improved resolution and sensitivity is demonstrated at arbitrary frequencies [2]. This paper, however, deals exclusively with ion isolation using dual isolation frequencies.

Ion trap resonances occur when an oscillating electric field couples energy into ion motion. They divide into broad categories: (1) the resonance occurring at the secular frequency of ion motion and (2) at harmonics of the secular frequency, (3) quadrupolar resonances, (4) resonances associated with sideband frequencies, and (5) nonlinear resonances [3–5]. The secular frequency, $\omega_{u,0}$ [6], is given by

$$\omega_{u,0} = \beta_u \Omega/2 \qquad (1)$$

where β_u is the dimensionless Mathieu parameter ($0 \le \beta_u \le 1$) for dimension u (x, y, r, or z) given as a function of the Mathieu q value [7], and Ω is the angular frequency of the driving radiofrequency (rf) waveform. The secular frequency is the frequency that dominates ion motion, particularly far from the Mathieu stability boundary [3]. Harmonics of the secular frequency can be observed at $2\omega_{u,0}$, $3\omega_{u,0}$, and so on.

Quadrupolar resonances can be accessed by application of a parametric excitation, with the primary parametric resonance at twice the secular frequency and higher order quadrupolar resonances at

$$\omega_{u,n} = |n + \beta_u|\Omega/K \quad -\infty < n < \infty,\ K = 1, 2, \ldots \qquad (2)$$

where n is an integer and K is the order of the resonance [8–10].

Sideband frequencies result from the interference of the rf driving frequency with the ion's fundamental secular frequency [3, 11] and are given by $n_u\omega_{u,n} \pm v\Omega$, where v and n_u are integers. Superposition of an odd-order field (e.g., hexapole) on the quadrupole field leads to observation of both even and odd harmonics and sidebands of those harmonics, whereas only odd harmonics and their sidebands are observed for even-order fields [3].

Lastly, nonlinear resonances result from the coupling of ion motion with higher-order multipole fields (e.g., hexapole, octopole, decapole, etc.) [3–5, 11–14]. These resonances are observed on iso-β lines (with no DC potential, as single q values); for example, $\beta = 2/3$ corresponds to a hexapole resonance and $\beta = 1/2$ corresponds to an octopole resonance. Typically, only even-order resonances are observed since odd-order resonances, which represent an asymmetric electric field, are not present due to electrode symmetry; however, they can be induced by application of an appropriate electric field or by modifying the electrode structure.

The general resonance equation [3–5, 11] is given by

$$n_r\omega_r + n_z\omega_z = v\Omega \qquad (3)$$

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where n_r and n_z are even integers for traps with symmetry in r and z, v is an integer, and ω_r and ω_z are the secular frequencies of ion motion in the r and z directions, respectively. The hexapole resonance is observed when $n_r + n_z = 3$, the octopole resonance is observed when $n_r + n_z = 4$, and so on, but n_r must be even for axially symmetric traps and n_z must be even in the presence of even-order fields but either even or odd for odd-order fields [11, 15].

Three general methods utilize ion trap resonances for mass-selection. The first is resonance ejection, which is a variant of the mass-selective instability scan [16]. In mass-selective instability, the rf amplitude is ramped linearly with time in order to eject and detect ions of increasing *m*/*z*. In resonance ejection [17, 18], a dipolar or quadrupolar AC potential is applied to the trap electrodes in order to produce a "hole" on the q axis of the Mathieu stability diagram. The hole makes the trajectories of ions whose frequencies of motion match the frequency of the AC unstable; thus, these ions are ejected. The rf amplitude is ramped in order to increase the secular frequencies of all ions in the trap (increasing β_u in Equation 1) until each comes into resonance with the applied AC, at which point the ions are mass-selectively ejected. Thus, mass selectivity is achieved because of differences in ion inertia, which cause ions to oscillate at different frequencies.

Double and triple resonance ejections are similar methods that achieve superior performance in terms of sensitivity and resolution. A double resonance technique is performed by making the frequency of the applied supplementary AC match the frequency corresponding to a nonlinear resonance point (e.g., $\beta_u = 1/2, 2/3$) [15]. A triple resonance is similarly performed by combining the two aforementioned techniques, that is, by simultaneously applying two different frequencies (i.e., the secular frequency and a sideband) that correspond to a nonlinear resonance point [19].

The activation step in collision-induced dissociation is a second general method that utilizes ion frequencies of motion in mass-selective operations [10, 18, 20, 21]. Typically, a low-amplitude supplementary AC potential with a frequency corresponding to that of ions of a particular *m*/*z* is applied (in either a dipolar or quadrupolar manner) to the trap for a short duration, causing the mass-selected ions to increase their amplitudes in the trap, occupy regions of greater electric field strength, and gain kinetic energy. Collisions with intentionally-introduced surrounding bath gas molecules such as helium or nitrogen then result in conversion of kinetic energy to internal energy and, hence, to ion fragmentation, from which structural information regarding the precursor ion can be deduced after product ion mass analysis.

Thirdly and lastly, ion trap resonances can be used for ion isolation, the topic of interest in this paper. One method of isolation is to ramp the rf amplitude up and subsequently down, ejecting ions whose *m*/*z* values are below and above the *m*/*z* value of interest, respectively [22]. In a second method, the ion of interest is placed at the apex ($a_z = 0.150$, $q_z = 0.781$ in the case of a 3D trap) of the Mathieu stability diagram by applying appropriate DC and rf potentials, thereby ejecting all other ions from the trap [23, 24]. Secular frequency scanning (also known as a "chirp"), in which the frequency of the supplemental AC signal is swept through all but that of some selected ion species, can also be used for ion isolation [22, 25–28]. However, the most commonly used technique implements the stored waveform inverse Fourier transform (SWIFT) [29], a method adopted from the Fourier transform ion cyclotron resonance mass spectrometer [30], to simultaneously eject ions of a broad range of *m*/*z* values except those of interest, using a complex waveform composed of multiple sinusoids of different frequencies. The waveform must be calculated beforehand as follows. First, the *m*/*z* values of the ions to be ejected are converted to their respective secular frequencies. The phases for these frequencies are purposely allotted according to a quadratic function to distribute the power of the waveform evenly throughout its application [31]. The frequencies and their amplitudes are then inverse Fourier transformed to obtain a time-domain waveform that must be generated by a direct digital synthesizer or similar hardware. Marshall and coworkers were the first to develop the theory of SWIFT isolation on the quadrupole ion trap [32] although the first experimental results were demonstrated at Purdue University [21]. It has also been shown that multiple nonadjacent ions, which require multiple "notches" (frequencies that are removed from the SWIFT waveform), can be isolated [33]. Lastly, amplitude and frequency modulation techniques, which reduce the number of frequencies needed for SWIFT waveforms, which in a typical isolation is some ~1000 frequencies, have been demonstrated [34, 35], though these waveforms still require calculation.

In this paper, we introduce a simple method of isolation performed by applying a dual-frequency waveform consisting of a combination of two sine waves of different frequencies. Dual frequency isolation is markedly simpler than the widely-used SWIFT isolation technique for isolation of ions of a single *m*/*z* value; despite the simplicity, it is shown that dual frequency isolation can resolve bromine isotopes with reasonable isolation efficiencies (up to ~60%). The method may find particular applicability in miniature mass spectrometers [36, 37], which benefit from small, simple, and power-efficient electronics.

Experimental

Ionization

All ions were generated by nanoelectrospray ionization (nESI) at 2 kV. Borosilicate glass capillaries (1.5 mm o.d., 0.86 mm i.d., 10 cm length) obtained from Sutter Instrument Co. (Novato, CA, USA) were pulled to an approximate o.d. of 5 μm using a Flaming/Brown micropipette puller from Sutter Instrument Co. (model P-97).

Chemicals

Didodecyldimethylammonium bromide was purchased from Sigma Aldrich (St. Louis, Missouri, USA), hexadecyl trimethylammonium bromide was purchased from Tokyo Chemical Industry Co. (Tokyo, Japan), and benzylhexadecyldimethylammonium chloride was purchased from JT Baker Chemical Co. (Phillipsburg, NJ, USA). p-Bromoaniline was purchased from Eastman Kodak Co. (Rochester, NY, USA). 2,4-Dichloroaniline and 4-chloroaniline were purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI, USA). EPA 508.1 herbicide mix (a mixture of alachlor, butachlor, simazine, atrazine, metolachlor, and hexachlorocyclopentadiene) was purchased from Sigma Aldrich (Bellefonte, PA, USA). Reagents were dissolved in HPLC grade methanol and then diluted in 50:50 methanol:H_2O with 0.1% formic acid to final concentrations of ~5 ppm.

Instrumentation

All experiments were performed using the positive ion mode on a Thermo LTQ XL linear ion trap mass spectrometer interfaced to an Orbitrap (San Jose, CA, USA), though the latter component was not used in these experiments. The normal scan rate of 60 μs/Da was used with automatic gain control turned on, but boundary ejection with a rf frequency of 1175 kHz was performed instead of using the instrument's built-in resonance ejection. The resonance waveforms normally generated by the LTQ's analog board were replaced by waveforms supplied from a Keysight 33612A arbitrary waveform generator (Newark, SC, USA). The generator was triggered at the start of the isolation period using the triggers in the LTQ Tune diagnostics menu. The ion to be isolated was typically placed at q = 0.2. A dual-frequency isolation waveform (amplitude typically 2–20 $V_{p\text{-}p}$ for each frequency) was used for ion isolation. The two sine waves generated were summed, output on a single channel, amplified using a Mini-Circuits (Brooklyn, New York, USA) rf power amplifier (model TIA-1000-1R8), and applied in a dipolar manner to the x electrodes of the linear ion trap. The waveform typically had a duration of 30 ms. The stated bandwidth of the rf amplifier was 0.5–1000 MHz, but signals down to ~60 kHz were able to be amplified, which limited the mass range in these experiments to ~*m*/*z* 800.

Results and Discussion

The general procedure for dual-frequency isolation in a quadrupole ion trap is given in Figure 1. The secular frequency of the ion of interest is sandwiched between two applied frequencies so that ions with *m*/*z* values below (Figure 1a) and above (Figure 1b) the *m*/*z* value of the ion to be isolated are ejected from the trap. There are many important considerations to take into account when choosing these frequencies as well as the q value at which the isolated ion is to be placed. In general, ions are easier to eject at lower q values because of the lower pseudo-potential well depth [38], thus allowing use of low AC amplitudes. At higher q values, potential well depth is higher, and thus higher AC amplitudes are needed. The performance of any isolation technique will vary widely with the q value of the ion to be isolated.

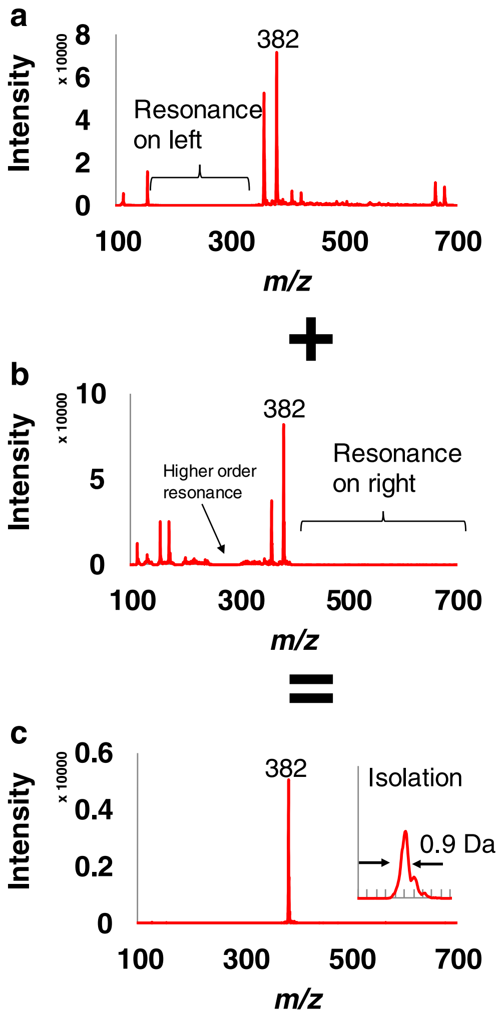

Figure 1. Dual resonance frequencies enable ion isolation in a quadrupole ion trap. The rf amplitude was set at ~287 $V_{0\text{-}p}$ while either a (**a**) 150 kHz, 7.97 $V_{p\text{-}p}$ or (**b**) 68.4 kHz, 5.98 $V_{p\text{-}p}$ waveform was applied during a 30 ms activation period, resulting in ejection of lighter and heavier ions, respectively, from the trap. Application of both waveforms simultaneously, as in (**c**), results in isolation of *m*/*z* 382. Note that (**c**) is the direct result of applying (**a**) and (**b**) simultaneously. The total amplitude of the isolation waveform is higher, and higher order fields (as in panel **b**) interact with the lower *m*/*z* ions, thereby helping to eject those leftover ions at low *m*/*z* in panel **a**

As the component that dominates ion motion, the secular frequency is the best candidate for these isolation waveforms because higher order resonances are generally weaker and thus more difficult to access. Figure 1c shows the result of applying a dual frequency waveform, which is the sum of the frequency at 150 kHz (β_x = 0.26, Equation 1) and another frequency at 68.4 kHz (β_x = 0.12, Equation 1).This places the ion's q value (0.2) between the two resonances. Once the frequencies were set, the AC amplitudes of each were adjusted so that ions with *m*/*z* values greater and less than that of the ion to be isolated (C^+, *m*/*z* 382) were ejected during the 30 ms isolation period. Because the amplitude of each sine wave is high, ions of a broad range of *m*/*z* values both higher and lower in *m*/*z* than the target ion are ejected. The sum of both sine waves, applied either simultaneously or successively, results in successful isolation of *m/z* 382. Thus, only two frequencies are required in this method, which is a dramatic reduction from current practice. Unfortunately, in this case ion isolation efficiency is only ~7.5%, which is quite low. As discussed later, better isolation quality leads to significantly worse isolation efficiency, and better results would be expected when placing the ion to be isolated at a high q value (e.g. 0.8). We should note that although it does not appear that the sum of panel a and panel b produces panel c because there are some low *m/z* ions left over in panel a, it was in fact the case that the sum of panel a and panel b resulted in successful isolation of *m/z* 382. The reason is that the maximum AC amplitude in panel c was *higher* than either panel a or panel b, which increases the range of *m/z* values that are ejected on both the high and low *m/z* sides of the ion to be isolated. Furthermore, the ions less in *m/z* than the target ion in panel a that are not ejected are likely excited nonetheless. The ions, therefore, experience a greater contribution of higher order fields (the higher order resonance in panel b, for example) so that when both frequencies are applied simultaneously, more ions of low *m/z* are ejected than in the single frequency case. A second reason for the ejection of more ions in panel c is the beat frequency that develops when two frequencies are summed together.

The general, applicability of dual frequency isolation is demonstrated in Figure 2, where cations (*m/z* 284, 360) of another pair of quaternary ammonium salts are easily isolated from other compounds in the mixture. Note that plot a is the full scan for both Figures 1 and 2. Each of the isolated ions shows increased resolution, presumably due to a reduction in space charge during the boundary ejection scan. Though slight fine-tuning of the frequencies and AC amplitudes was needed in order to achieve these results, the method does not require the calculation and synthesis of a broadband SWIFT waveform, nor does it require a direct digital synthesizer of similar waveform generator, reducing instrument complexity and computational time. Isolation efficiency for each of the ions was ~33% for *m/z* 284 and ~3% for *m/z* 360. The latter efficiency is lower likely because the other analyte ion (*m/z* 382) is much closer to *m/z* 360.

The tradeoff with this method is that higher waveform amplitudes are required to promote ejection over a broad mass range, particularly at high q (low mass ions) since the pseudopotential well depth increases with both q and rf amplitude [38]. So why does a higher waveform amplitude effect broadband ejection of ions? To answer this question, we must first understand the conditions under which ions resonantly absorb energy from an excitation at a given frequency. Resonance absorption curves can be found in reference [39]. As shown in that paper, ions absorb energy even when excitation is slightly off resonance, giving absorption curves that are approximately Gaussian. Since each ion would have a resonance absorption curve centered at its respective secular frequency, and each has an approximately Gaussian distribution (with some asymmetry), a high AC amplitude can then be used to interrogate a large swath of ions, thereby allowing us to isolate an ion using two frequencies.

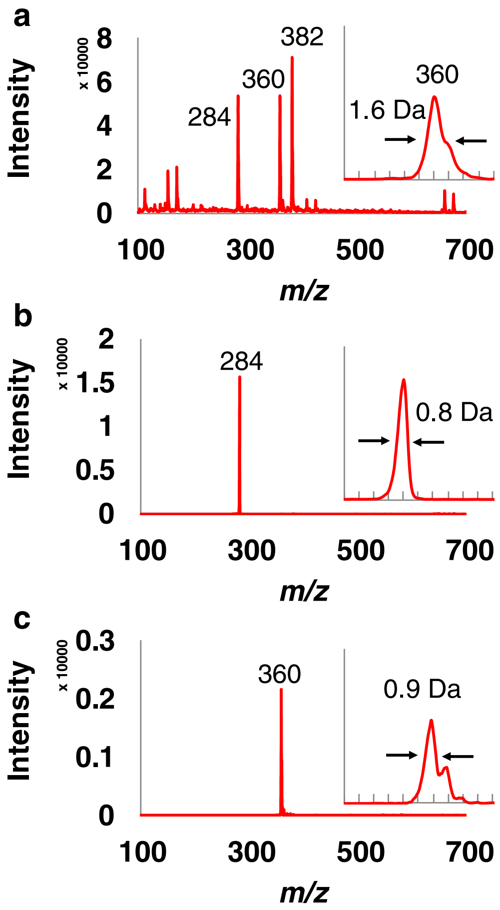

Figure 2. Ion isolation in a linear ion trap using dual resonance frequencies. Spectrum (**a**) shows boundary ejection mass spectrum of a mixture of three quaternary amines (*m/z* 284, 360, and 382), and (**b**) and (**c**) show isolation of *m/z* 284 and 360 using dipolar application of a dual frequency resonance waveform during a 30 ms isolation time just before the analytical mass scan. Experimental details are as follows: LTQ linear ion trap mass spectrometer, (**a**) boundary ejection using a scan rate of 60 μs/Da, (**b**) and (**c**) boundary ejection after application of a 30 ms waveform with frequency components (**b**) 68.4 kHz, 3.26 $V_{p\text{-}p}$, and 149 kHz, 7.12 $V_{p\text{-}p}$, (**c**) 68.4 kHz, 5.60 $V_{p\text{-}p}$, and 150 kHz, 7.97 $V_{p\text{-}p}$. The rf amplitude was ~200 $V_{0\text{-}p}$ in (**b**) and ~270 $V_{0\text{-}p}$ in (**c**). All spectra are averaged from ~30 scans

In our case, high AC amplitudes were obtained with a broadband rf amplifier. One could also add more frequency components while keeping the amplitude of the waveform low. For example, the ejection of low-mass ions using two frequencies and ejection of high mass ions with a single frequency was investigated as summarized in Figure 3. Without using an rf amplifier, the dual frequency isolation method struggles to eject ions lower in mass than the selected ion, presumably due to greater potential well depth, making broadband ejection more difficult. However, addition of a third frequency component (Figure 3b) improves the performance of the method. Isolation efficiency in this case was improved to ~50% by using two frequencies at low *m/z* instead of one.

The ability to isolate isotopic forms of a molecular ion from each other is a challenge for a dual frequency method because (1) ion attenuation is quite large when isolating adjacent species (discussed later), and (2) the secular frequencies of isotopes

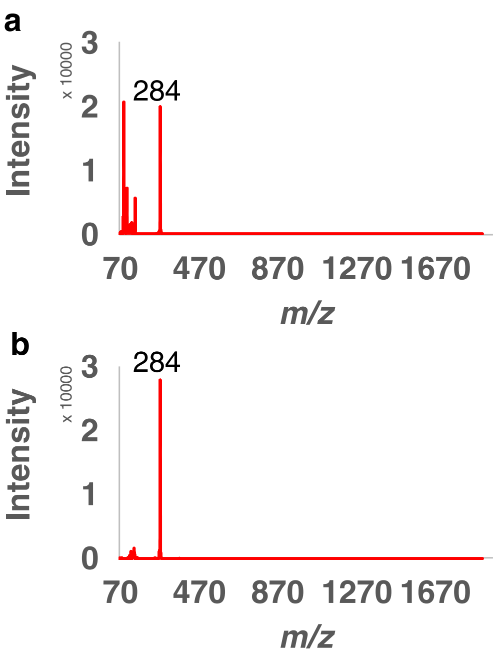

Figure 3. Dual and triple frequency isolation with restriction to low AC amplitudes. In (**a**), *m/z* 284 was isolated during a 30 ms period during which a dual frequency isolation waveform consisted of 129 kHz, 3 $V_{p\text{-}p}$, and 26 kHz, 6.2 $V_{p\text{-}p}$. For (**b**) the isolation waveform consisted of three frequencies: 26 kHz, 0.7 $V_{p\text{-}p}$, 144 kHz, 8 $V_{p\text{-}p}$, and 278 kHz, 8 $V_{p\text{-}p}$. In both experiments, *m/z* 100 was placed at $q_x = 0.7$ during isolation

are very close together. Isotope isolation is demonstrated in Figure 4, where a mixture of 4-chloroaniline, 2,4-dichloroaniline, and p-bromoaniline were analyzed by boundary ejection (Figure 4a). Figure 4b shows the isolation of both isomers of p-bromoaniline from the mixture using frequencies corresponding to $\beta_x = 0.12$ (69 kHz) and $\beta_x = 0.25$ (149 kHz). Isolation efficiency for this pair of ions was nearly 100% despite the complexity of the mixture. The method can also resolve the ^{81}Br isotope from ^{79}Br, as shown in Figure 4c, which was accomplished by slightly shifting the applied frequencies. An alternative is to change the amplitude of one or both of the frequency components. Signal attenuation in Figure 4c is, as expected, worse than in Figure 4b because the isolation resolution is higher, giving an approximate isolation efficiency of ~60% for *m/z* 172.

The amount of time for which a waveform needs to be applied was investigated also (Figure 5a). For 30 μs of ion isolation, an isolation width of ~70 *m/z* was obtained, which decreased to 40 *m/z* and 27 *m/z* for 300 μs and 3 ms, respectively. The best results were obtained for 300 ms of waveform application, but only small improvements were observed beyond 30 ms of isolation. Note that the conditions for this experiment were somewhat more lenient than in Figure 2, giving a minimum isolation width of ~14 *m/z* (129 kHz, 7 $V_{p\text{-}p}$ and 50.6 kHz, 3.7 $V_{p\text{-}p}$, variable isolation time).

The main concern with any isolation method is isolation efficiency, or how many of the ions of given *m/z* are retained in the trap after isolation. Data are shown in Figure 5b. The isolation width, in this case, was changed by varying the amplitude of either the low frequency or high frequency sine wave. The isolation width increased when the amplitude of either sine wave was decreased. In order to obtain an isolation width of 1 *m/z*, in this particular case, isolation efficiency decreases to a mere 3.4% (as in Figure 1c). However, if a more modest isolation window is set, 10 *m/z* for instance, up to 80% of the ions of that *m/z* are retained, a marked improvement. When we compare the effect of varying the amplitude of the lower frequency (ejecting high *m/z*) and varying the amplitude of the higher frequency (ejecting low *m/z*), it becomes clear that most of the loss in isolation efficiency is due to the lower frequency component. We attribute this phenomenon to the asymmetry in resonance absorption curves, which tend to extend further to lower frequencies than to higher frequencies [39].

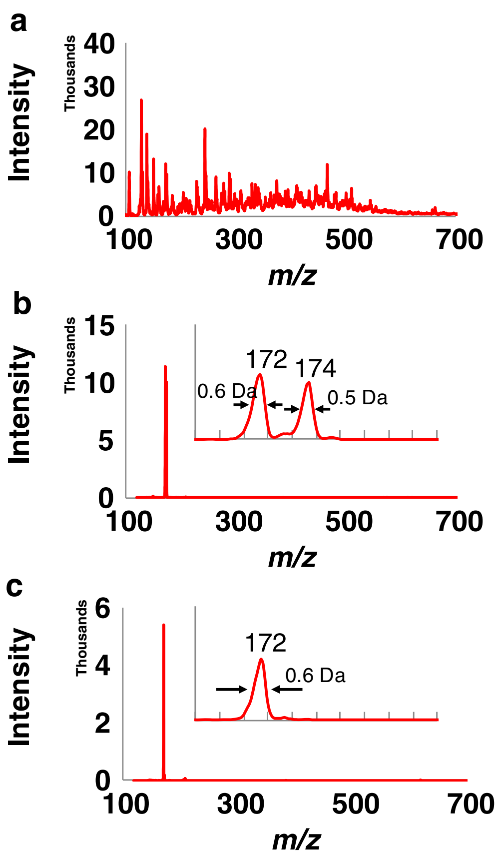

Figure 4. Isolation of bromine isotopes using dual frequency isolation: (**a**) shows full mass spectrum of a mixture of 4-bromoaniline, 4-chloroaniline, and 2,4-dichloroaniline obtained by boundary ejection, (**b**) shows isolation of both isotopes of 4-bromoaniline, and (**c**) shows isolation of only one isomer. Isolation waveform was 69 kHz, 16.96 $V_{p\text{-}p}$, and 149 kHz, 2.63 $V_{p\text{-}p}$ for (**b**) and 69 kHz, 16.96 $V_{p\text{-}p}$, and 157 kHz, 2.63 $V_{p\text{-}p}$ for (**c**). The rf amplitude was 370 $V_{0\text{-}p}$ in (**b**) and (**c**)

Ion isolation is particularly useful for removing chemical noise when examining complex mixtures. Figure 6a shows the full scan boundary ejection mass spectrum of a mixture of herbicides and their metabolites, with the inset spectrum showing the poor resolution obtained as seen in the peak shape for *m/z* 481, which is the base peak. Isolation of this analyte using a

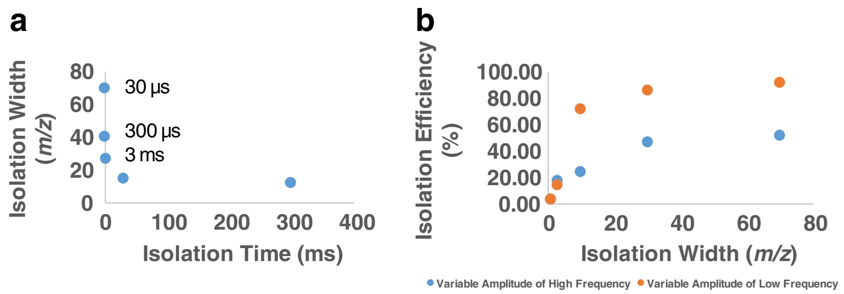

Figure 5. Performance characteristics of dual frequency ion isolation: (**a**) isolation width versus isolation time, and (**b**) isolation efficiency versus isolation width. In (**a**), *m/z* 360 was placed at q = 0.2 and isolated using dual resonance frequencies, as in Figure 2c. In (**b**), *m/z* 382 was placed at q = 0.2 and isolated using dual resonance frequencies, as in Figure 1c, and isolation width was changed by altering the amplitude of either the high or low frequency waveform

dual frequency sinusoidal waveform at 66 kHz, 20.58 $V_{p\text{-}p}$, and 254 kHz, 9.63 $V_{p\text{-}p}$, with an rf amplitude of 370 $V_{0\text{-}p}$, noticeably improves mass resolution. More importantly, *m/z* 292, which is likely a chlorinated metabolite of one of the herbicides and a minor component with very little signal intensity in the full scan, is isolated with application of a 30 ms dual frequency waveform (30 ms isolation waveform of 64.1 kHz, 3.6 $V_{p\text{-}p}$, plus 166 kHz, 17.28 $V_{p\text{-}p}$, rf amplitude of 287 $V_{0\text{-}p}$). Thus, the dual frequency isolation method can, despite the simplicity of the procedure, be used to isolate both high and low abundance ions with the ability to isolate isotopic peaks from one another. We again note that isolation tends to be difficult at low q. Even in our "worst case scenarios" (i.e., isolation at low q), isolation efficiencies of >60% can be obtained. This efficiency should improve at higher q values.

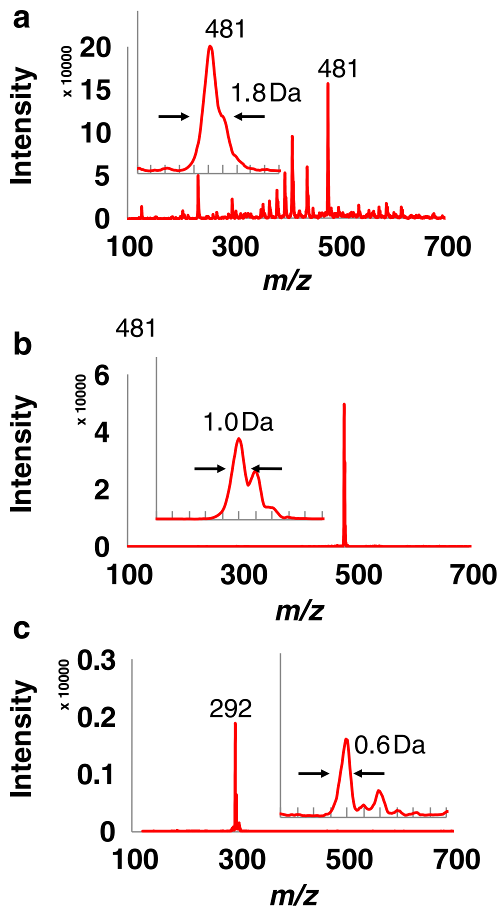

Figure 6. Application of dual frequency isolation to complex mixture analysis: (**a**) shows the full scan boundary ejection spectrum of a mixture of herbicides and their metabolites (EPA 508.1 herbicide mix), whereas (**b**) shows dual frequency isolation of a major component (*m/z* 481) and (**c**) shows isolation of a minor component (*m/z* 292). Experimental details are as follows: (**b**) 30 ms isolation waveform of 66 kHz, 20.58 $V_{p\text{-}p}$, and 254 kHz, 9.63 $V_{p\text{-}p}$, rf amplitude of 370 $V_{0\text{-}p}$; (**c**) 30 ms isolation waveform of 64.1 kHz, 3.6 $V_{p\text{-}p}$, plus 166 kHz, 17.28 $V_{p\text{-}p}$, rf amplitude of 287 $V_{0\text{-}p}$

In principle, the two frequencies used here could be applied orthogonally, as in reference [40], which describes the application of a single frequency on the x electrodes and a second frequency on the y electrodes for removing ions of higher and lower *m/z* than the ion being detected, thereby increasing resolution with a quadrupole mass filter. There are two complications, however, to applying such a method to a linear ion trap: (1) a supplementary AC would have to be coupled to the rf for application on the y rods (usually AC and rf are only coupled onto the x rods), and (2) the secular frequencies of ions in x and y would be different if the radii in those respective dimension were different. Nonetheless, we imagine a variant of resonance ejection in which orthogonal frequencies, one for ion ejection out of the slits in the x rods and the other for ion ejection into the y rods, which could increase resolution. Such a technique would be similar to rhombic ion ejection [41].

The dual-frequency isolation method demonstrated in this paper offers simplicity while maintaining reasonable performance in terms of signal attenuation and isolation resolution. Though SWIFT is more flexible and offers better performance, smaller instruments may benefit from a simpler technique. Other isolation methods [22], though less commonly used, are also more complex than the current technique or do not offer good performance. For example, a forward and subsequent reverse rf ramp suffers from poor isolation quality, particularly during the reverse ramp. Rf/DC isolation can be used (i.e., a trap can be operated as a quadrupole mass filter), but DC offsets must be coupled to the oscillating rf and AC voltages. A notched secular frequency scan ("chirp"), in which an ion is isolated by introducing a 180° phase shift at that ion's secular frequency [28], is as simple as the current method, but SWIFT is more efficient in terms of time, and both waveforms would still require calculation and synthesis using direct digital synthesis technology.

Conclusion

We have introduced a simple method of ion isolation that uses a high-amplitude dual frequency sinusoidal waveform consisting of frequencies centered above and below the secular frequency of the ion to be isolated. This method joins an expanding list of isolation techniques, including SWIFT, rf amplitude ramps, resonance ejection, and secular frequency scanning.

The new capabilities demonstrated here complement the suite of techniques described in this and the associated two papers. The other two methods address successive resonance ejection and multigenerational collision-induced dissociation for broadband fragmentation. The trio as a whole simplifies ion trap operation, expands the range of scans possible on such devices, and brings much-needed performance improvements to miniature mass spectrometers.

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