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Square wave modulation of a mirror lens for ion isolation in a Fourier transform electrostatic linear ion trap mass spectrometer

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ABSTRACT

Isolation of ions is a critical step in tandem mass spectrometry experiments. In electrostatic linear ion trap mass spectrometers, isolation is typically performed either using a timed ion selector, or by using a periodic electric field orthogonal to the axis of ion motion. In the latter case, the frequency of the field is matched to an ion of interest and the phase is such that the field is zero when the ions of interest are passing through the affected region. The periodic field method has the advantage that it is easier to isolate a single ion from a complex mixture. Here we describe an isolation method that produces essentially identical results to the orthogonal field method, but does not require the addition of any electrodes to the ion path. Instead, the periodic signal (a high voltage square wave) is applied to a lens that is a constituent of one of the ion mirrors. The square wave alters the energy of contaminant ions causing them to be lost from the trap. We demonstrate isolation of ions from a complex mixture using the square wave modulation technique. We also demonstrate an isolation resolution of 200 by isolating isotopes of a small molecule. We also characterize the performance of this method as a function of amplitude and time. An amplitude as low as 200 V applied for 1 ms can result in high-quality isolations using this method. We also discuss important considerations for those wishing to implement the method on other instruments.

1. Introduction

Tandem mass spectrometry [1] (MS/MS) entails the process of isolating ions of a specific mass-to-charge (m/z) ratio, chemically processing the isolated precursor ions, and then measuring the masses of the product ions. MS/MS is a widely used method for increasing the sensitivity and specificity of mass spectrometric analysis. MS/MS can also provide chemical information about the precursor such as structure and reactivity. The ever-growing variety of processing methods (e.g., reaction types, dissociation methods, etc.) ensures that MS/MS will continue to expand its capabilities in addressing important measurement problems.

The electrostatic linear ion trap (ELIT) [2–4] is a relatively new mass analyzer that consists of two reflectrons positioned facing each other at opposite ends of a field-free region. Ions of fixed energy are introduced axially and 'bounce' back-and-forth between the reflectrons, which confine the ions in both the radial and axial dimensions. Mass measurement can be performed either of two ways: either the ions can be released to a detector where a time-of-flight (ToF) measurement is made, [2] or the ions can be monitored nondestructively using an image charge pickup electrode while they remain trapped. In the latter case, the signal from the pickup electrode is Fourier transformed (FT) to yield the m/z dependent oscillation frequencies of the trapped ions [5].

ELIT analyzers share characteristics with both ToF analyzers and FT analyzers (such as Fourier transform ion cyclotron resonance (FTICR) and orbitrap mass analyzers) that can be exploited to isolate ions. For example, in ToF analyzers, the ions are dispersed in space by an amount that increases with increasing flight time. Therefore, ions may be isolated by applying a properly timed voltage pulse to a deflector such as a Bradbury–Nielsen gate [6] located along the flight path. The start time and duration of the pulse are chosen such that only the ions of interest are allowed to pass through the gate. This isolation method is commonly used in tandem time-of-flight (ToF/ToF) instruments [7–9]. An advantage to this method is that isolation can be performed on a short (tens of milliseconds at most) timescale. The short time required makes this isolation method popular with groups seeking to measure the masses of short-lived radionuclides [10–13]. These groups use ELIT devices (which they call multi-reflection time-of-flight or MR-ToF)

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as opposed to more traditional ToF designs (linear or single reflectron) presumably because an ELIT can provide long (and tunable) flight times from a small form factor. We have employed similar methodology to isolate precursor ions as part of a scheme for doing nondestructive MS/MS [14].

However, a complication arises when using the above method with an ELIT: because the ions repeatedly retrace the same path, the separation between two ions will not perpetually increase with flight time. Rather, the separation will grow to a maximum determined by the dimensions of the trap, and then shrink back to zero as the faster ions catch up to and 'lap' the slower ions. This process repeats itself with a frequency determined by the mass difference between the two ions. Any two ions can be isolated by waiting the proper amount of time such that maximum separation is achieved, but isolation becomes increasingly difficult as additional ions of different masses are added to the trap. Pinpointing a moment in time in which designated precursor ions are spatially separated from all other ions of different m/z ratio becomes increasingly problematic as the number of distinct mass ions increases.

The problem described above is inherent to analyzers in which ions retrace the same path. One such analyzer is the FTICR. In an idealized ICR cell, the ions travel around a ring the radius of which typically does not exceed a few centimeters. Despite this low degree of physical separation of ions within the cell, isolations are routinely performed using techniques like frequency sweep excitation [15,16] and stored waveform inverse Fourier transform (SWIFT) [17,18]. These techniques work because they do not rely on physical separation of the ions; rather, they involve matching frequency components of an excitation signal to motional modes of undesired ions within the cell. These ions then absorb power from the excitation waveform and gain energy until they are lost from the cell leaving behind the isolated precursor ions. One isolation method has been described that is similar in spirit, but for use with ELIT analyzers. Toker and coworkers added a pair of electrodes to the field-free region of an ELIT that could be used to generate an electric field orthogonal to the axis of ion motion [19]. Ions could be isolated by applying a square wave to these plates with frequency and phase matched to the desired precursor ions. Under these conditions, the electric field between the plates would always be zero when the ions of interest were passing through, but undesired ions would eventually find themselves between the plates when the electric field was nonzero. This would alter the trajectories of the undesired ions that would result in their loss through collisions with electrodes, leaving the desired precursor ions isolated. This method was previously used to isolate ions trapped in an electrostatic storage ring [20]. This method has since been implemented in several ELIT devices intended for purification of short-lived radionuclides [10]. In these devices, the orthogonal field is used to isolate only those ions that have completed a specific number of cycles (typically isobars); a Bradbury–Nielsen gate is then used to isolate a specific isobar. In this manner, isolation of a single isobar from a complex mixture can be achieved in the shortest time.

The method we describe here serves the same purpose as the orthogonal field isolation method, but is achieved without adding electrodes to the ELIT analyzer. Instead, we apply the square wave to a lens that is a constituent of one of the reflectrons. The principal hardware requirement is a fast, high-voltage switch. Such switches are already required for ELIT analyzers because they are used to control the ingress and egress of ions from the device. In some cases the hardware may already be in place and the only thing left to do would be to modify the signal controlling the switch.

We are not the first to modulate the potential applied to a mirror lens of an ELIT in order to manipulate ion motion in the device. Rahinov and coworkers superimposed a low amplitude RF signal on top of the static potential applied to a mirror lens of their ELIT. This signal was used to prevent dephasing of ions with a specified m/z enabling their selective detection by image charge monitoring [21]. These ions were not truly isolated, however, as the contaminant ions remained in the trap, albeit undetectable. Thomson patented a device in which a periodic waveform is used to increase the energy of target ions trapped in an ELIT [22]. Once their energy is high enough, the ions are ejected to a second trap and thereby isolated. Also, in a related electrostatic trapping device known as an autoresonant trap mass spectrometer (ART-MS), an RF signal is applied to one of two repulsive endcap electrodes in order to synchronize the motion of ions of a specified m/z [23,24]. The frequency is then ramped down in order to pump energy into the ions and eject them to a detector. Our isolation method makes similar use of voltage modulation to manipulate the energy of contaminant ions in order to remove them from the trap. Below we describe the implementation of our method and the mechanism that gives rise to isolation. We also characterize the performance of the method and discuss practical issues pertaining to the method's implementation on other instruments.

2. Experimental

2.1. Materials

The cesium iodide sample was prepared by dissolving the analyte to a concentration of 9 mM in a solvent of 49.5% water, 49.5% methanol, 1% acetic acid. The 5-bromoisoquinoline sample was similarly prepared to a concentration of 100 μM. A sample containing tetraoctylammonium (TOA) bromide at a concentration of 30 μM and tetrabutylammonium (TBA) bromide at 70 μM was prepared using the same solvent. Cesium iodide, 5-bromoisoquinoline, TOA, and TBA were purchased from Sigma–Aldrich (St. Louis, MO). Methanol and glacial acetic acid were purchased from Malinckrodt (Phillipsburg, NJ). Water was purified with a water purifier (D8961, Barnstead, Dubuque, IA) prior to use.

2.2. Mass spectrometry

The mass spectrometer has been described previously [14]. Briefly, sample solution is loaded into a pulled glass capillary placed in front of the sampling orifice. An electrospray is created by applying high voltage to a platinum wire in contact with the solution [25]. The ions are transported to a quadrupole linear ion trap where they are accumulated before being pulsed into the ELIT. Each reflectron of the ELIT consists of seven lenses (see Fig. 1). The voltages applied to the lenses during trapping are (outermost to innermost): 2450, 1700, 1000, 0, −1910, −2060, 0 V. In the ELIT, the ions oscillate between two reflectrons and their image charge signal is generated using a central pickup electrode. The pickup electrode is connected to a charge sensitive preamplifier (CoolFET, Amptek, Bedford, MA). The output of the preamplifier was amplified and shaped using a Gaussian shaping amplifer (CR-200–500 ns-INST, Cremat, Watertown, MA). The output of the shaping amplifier is digitized using a PCI-based high speed digitizer card (CS1621, Gage Applied Technologies, Lachine, QC, Canada). Any square wave modulation is applied beginning when the ions enter the ELIT. In these cases, data acquisition is delayed until after the modulation is deactivated. The acquisition time is sufficient to allow the signal to decay into the noise. The time-domain data are zero-filled to double their original length before being subjected to fast Fourier transformation to generate a mass spectrum. All spectra shown below are averages of ten acquisitions.

2.3. Square wave modulation

A schematic illustrating the application of the square wave is given in Fig. 1. A power supply (P02HA30, Acopian Technical,