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Fourier Transform Time-of-Flight Mass Spectrometry in an Electrostatic Ion Beam Trap

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We report on the application of an electrostatic ion beam trap as a mass spectrometer. The instrument is analogous to an optical resonator; ions are trapped between focusing mirrors. The storage time is limited by the residual gas pressure and reaches up to several seconds, resulting in long ion flight paths. The oscillation of ion bunches between the mirrors is monitored by nondestructive image charge detection in a field-free region and mass spectra are obtained via Fourier transform. The principle of operation is demonstrated by measuring the mass spectrum of trapped Ar⁺ and Xe⁺ particles, produced by a standard electron impact ion source. Also, mass spectra of heavier PEG_nNa⁺ and bradykinin ions from a pulsed MALDI ion source were obtained. The long ion flight path, combined with mass-independent charge detection, makes this system particularly interesting for the investigation of large molecules.

Initially, due to its low resolution, time-of-flight mass spectrometry (TOF-MS) was regarded as a less promising technique compared to other techniques such as quadrupole mass spectrometry (QMS) and Fourier transform ion cyclotron mass spectrometry (FTICR-MS). The low resolution originated in the fact that the ionization techniques used in TOF-MS, such as electron impact and laser ionization, produced ions with large temporal, spatial, and energy spread, which resulted in a spread in the arrival time. With the advent of schemes for the correction of energy-dependent flight time errors, by time lag focusing¹ and compensating mirrors,² time-of-flight instruments became increasingly common in various fields of mass spectrometry. The main advantages of TOF-MS techniques lie in fast acquisition time, high throughput, and their virtually unlimited mass range. The latter became particularly important, after methods for the production of ions of large biological molecules in the gas phase were developed by Karas and Hillenkamp (matrix-assisted laser desorption/ionization, MALDI)^{3,4} and by Fenn and co-workers

(electrospray ionization, ESI).⁵ These ionization techniques have been adapted to TOF-MS using orthogonal injection for ESI (e.g., ref 6 and references therein) and delayed extraction (DE) for MALDI.^{7,8} With the increasing demand for studying even larger molecules up to the megadalton range, the challenge of mass spectrometry shifted from the ion production step to mass separation and detection. TOF development then focused on the improvement of mass resolution and sensitivity for these large molecules. Improvements in the resolution in TOF instruments are usually made by increasing the length of the flight path. However, simply using longer flight tubes soon reaches practical limits. This can be avoided by folding the flight path into the same physical space before the ions are steered onto a detector. Folding the flight path is usually accomplished by the use of ion mirrors, as introduced by Mamyrin et al.² for flight time correction in a single reflecting reflectron-TOF. Several papers on multireflecting instruments based on ion mirrors have been published.^{9–12} In these instruments, grids are used to obtain homogeneous electric fields, and the resolution can be increased, at the cost of low transmission for several passes through the grids.^{13,14} In a recent publication, Piyadasa et al.¹⁵ reported on a multireflecting instrument, where a resolution of $R = m/\Delta m = 31\,000$ for bovine insulin ($m/z = 5734$) was obtained. In that study, DE^{7,8} was also used to enhance mass resolution. A gridless multipass reflectron that avoids the problem of low transmission was suggested by Wollnik.^{16,17}

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Besides the length of the flight path, another main problem of mass spectrometry of large molecules relates to the detection step itself. The commonly used detectors that are based on secondary electron emission (e.g., microchannel plates, MCP) are characterized by an exponential falloff in detection efficiency for decreasing velocities.¹⁸ Improved detection sensitivity has been obtained using an ion to photon conversion device¹⁹ and cryogenic detectors.^{20,21} Nondestructive charge detection is much less sensitive for smaller ions than MCP detectors, but has higher detection efficiency above a certain mass-to-charge ratio, which is $\sim 10\,000$. Charge detection has been used for MALDI-TOF^{22–24} and ESI-TOF^{25–27} and is the standard technique in FTICR²⁸ and in Schottky mass spectrometry.^{29,30}

In principle, multiple reflecting TOF instruments can provide long flight paths with mass-independent detection sensitivity. The ultimate limit for a multiple reflecting instrument is to trap the molecules for an infinite number of oscillations. The detection is preferentially achieved by applying a nondestructive detection technique on every pass through the detector. An instrument, in which ions are infinitely trapped between two focusing mirrors in analogy to an optical resonator, has been developed in our laboratory and the detailed design as well as the conditions for stability have been published.^{31–33} The gridless structure allows storage of ions up to seconds, with the lifetime determined solely by collisions with residual gas molecules. The first experiments exploited the trapping mode of this instrument and were directed toward studying of metastable-state lifetimes of atomic and molecular ions.³⁴ Later on, Benner used an instrument design similar to ours for trapping and detection of single, highly charged

DNA molecules.³⁵ Though Benner reported trapping of ions, it is unclear whether the ion mirrors used in his instrument fulfill the focusing conditions, which are the key point for long flight path and long storage time of ions. In a recent paper by Rockwood,³⁶ the principle of operation of an ion trap in analogy to an optical resonator was again elaborated, mainly based on trajectory simulations. In the present study, we demonstrate the ability of our gridless electrostatic ion beam trap for general mass spectrometric applications. Fourier transform techniques are applied for mass determination from ion bunches oscillating on linear trajectories. We demonstrate the trapping stability and measure the lifetime of an argon ion beam stored in the trap. Mass spectrometric measurements are performed on ions from a chopped argon and xenon ion beam and from a MALDI ion source. For the latter case, poly(ethylene glycol) (PEG) and the peptide bradykinin (BK) were chosen with mass up to 1060 amu. Delayed extraction is applied in the MALDI experiments to improve mass resolution.

EXPERIMENTAL SECTION

The principle of operation of the electrostatic ion trap has been described in previous publications and will be only briefly described here.^{31,33} The motion of particles in an electrostatic field can be described similarly to the propagation of light in a medium, where the index of refraction is analogous to the square root of the electric potential. In an optical resonator, photons are trapped, if certain conditions for the length of the resonator and the focal properties of the end mirrors are fulfilled. Such a setup is the key for the operation of lasers, and its principles are well known.³⁷ In analogy to an optical resonator, a Gaussian beam of ions can be trapped between two symmetric mirrors if the following condition is fulfilled:^{31,33}

$$L'/4 \leq f_1 \leq \infty \quad (1)$$

where L' is the effective distance between the mirrors and f_1 is their focal length. Ions stored in the trap oscillate on stable trajectories between the confining mirrors with frequencies proportional to the square root of the charge-to-mass ratio:

$$f \propto \sqrt{z/m} \quad (2)$$

Therefore, the mass of singly charged particles can be obtained by measuring their oscillation frequency; for multiply charged particles their charge has to be measured as well. However, if the various isotopes from a single species can be resolved, then the charge can be determined from the isotope frequency spacing. A schematic view of our ion beam trap is shown in Figure 1. Mechanically, it consists of two identical stacks of electrodes, mounted on a rod assembly. The center of the trap is field free and at ground potential. The potentials on the electrodes linearly increase from E_1 to E_5 , with the electrode E_1 at ground potential. Electrodes Z_1 , Z_2 , and E_1 operate as an asymmetric Einzel lens. The mirrors confine the ions in the longitudinal direction, and the Einzel lens voltage is chosen so that the trapping condition,

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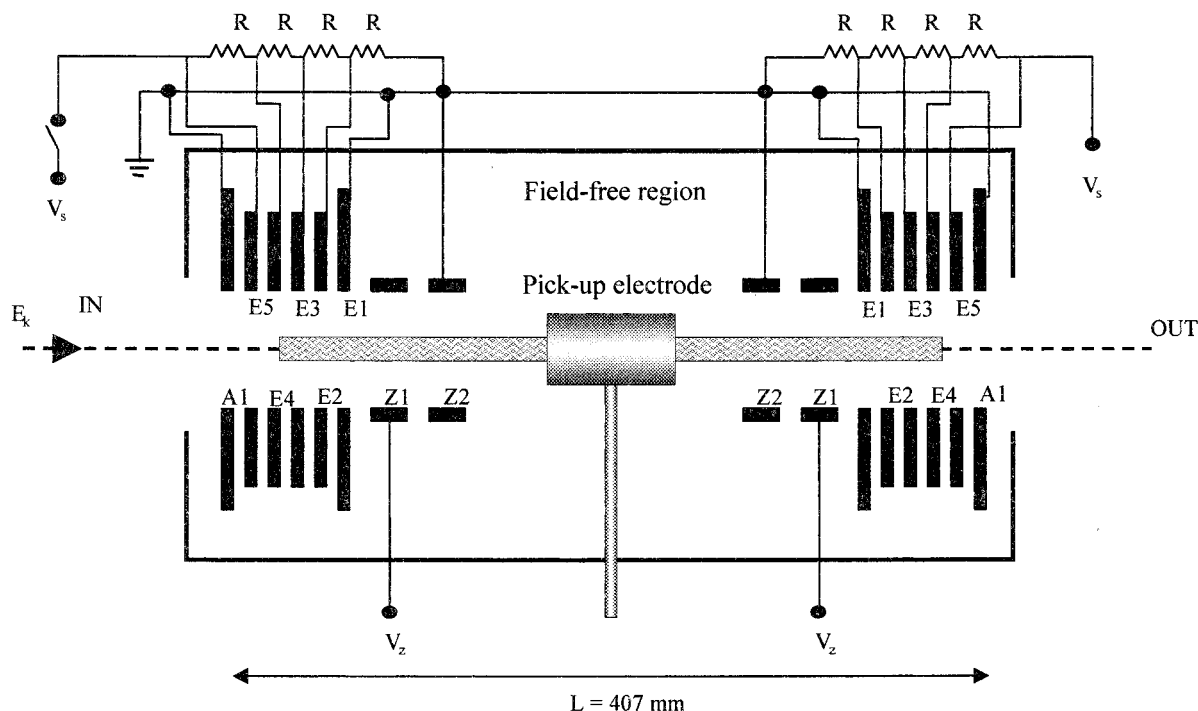


Figure 1. Schematic view of the ion trap. The switched and unswitched mirrors can be interchanged, as required. See Figure 2.

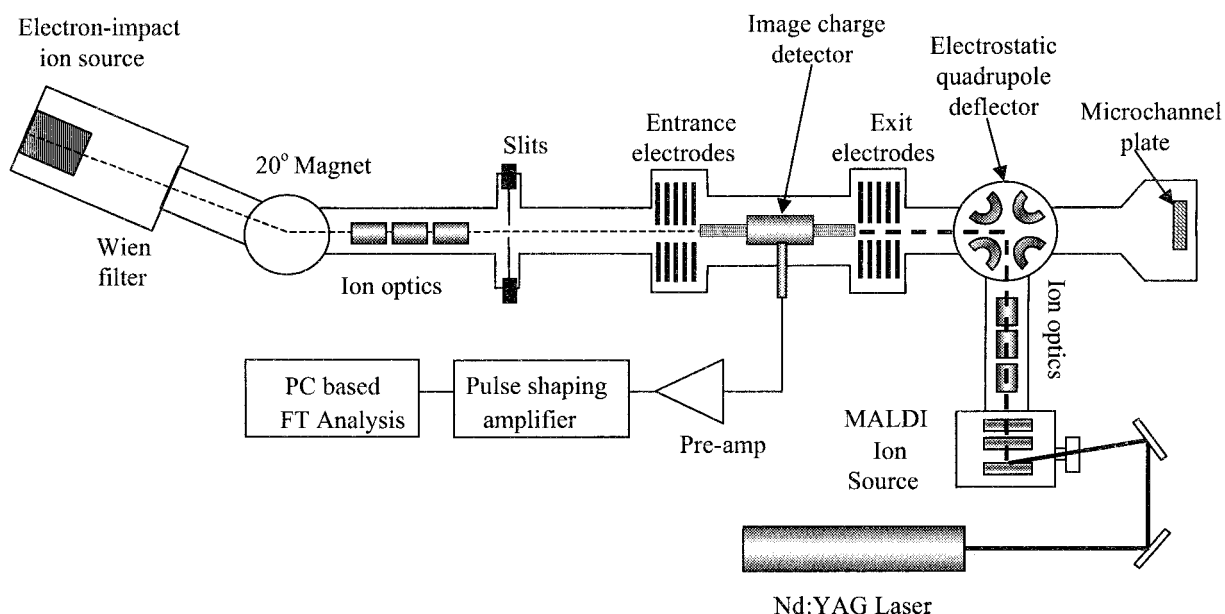


Figure 2. Experimental setup. The length of the image charge detector is 80 mm and its inner diameter is 20 mm.

eq 1, is fulfilled. The geometrical design of the ion trap and the potential settings have been developed using Simion³⁸ for ion trajectory simulations. Ions are injected into this assembly along the axis from either side of the trap. Initially, before injecting ions, the entrance mirror is grounded, while the exit mirror is kept at high voltage.

Bunches of atomic and molecular ions from either an electron impact or MALDI source are injected into the trap. After a bunch has entered the trap, the potentials on the entrance mirror electrodes are switched on, reaching values equal to the potential settings of the electrodes on the exit side. After switching the voltages, the ions travel back and forth between the two mirrors. This trapping mode has been studied and more details are

published elsewhere.^{32–34} The experimental setup of the beam line is shown in Figure 2. The lifetime of stored ions is limited only by collisions with the residual gas in the trap. The vacuum chamber is pumped by a cryo pump (2000 L/s) and pressures of a few 10^{-10} Torr can be reached without baking the system.

A cylindrical pickup electrode for charge detection is mounted at the center of the trap. Ion bunches passing through this electrode induce an image charge which is amplified by a low-noise charge-sensitive preamplifier and shaped by a second amplifier. The signal is digitized and Fourier transformed (FT) on-line to obtain a frequency spectrum. Further, an MCP detector

(38) Simion V.6.0. ion source software.

is mounted at one end of the trap, ~ 1.2 m away from its center, to simultaneously detect neutral particles leaving the trap.

Two types of ion sources are used for characterization of the mass measurement. Singly charged Ar^+ and Xe^+ ions produced by an electron impact ion source are accelerated to several kiloelectronvolts. After mass selection using a Wien filter and a 20° magnet, the ion beam is focused and collimated before it enters the trap along its axis. The beam can be chopped by pulsed deflection electrodes. Faraday cups that can be moved into the beam line on both sides of the trap aid in alignment of the beam. This ion source was used to inject ions of a single and well-known mass in order to calibrate the mass spectrometer. To study larger molecules, a home-built MALDI source³⁹ was coupled to the beam line. The MALDI sample is held in the source directly on the repeller plate of the two stage extraction optics by a spring-locked assembly. The unfocused laser beam was confined to a diameter of 1.5 mm by a circular aperture and hit the MALDI sample at an angle of incidence of 65° . The third harmonic of a Nd:YAG laser (pulse width 8 ns) at a repetition rate of 10 Hz is used as the laser source, and the source is equipped for delayed extraction. Beam shaping and steering is performed in the ion source by deflection plates and an Einzel lens. The ions enter an electrostatic quadrupole where they are deflected toward the ion trap. For the MALDI matrix, 2,5-dihydroxybenzoic acid (DHB) is used, which is prepared as a saturated solution in a mixture of ethanol and deionized water (1:9). For the analyte solutions, PEG (average $m/z = 400$) or BK ($m/z = 1060$) were mixed with deionized water (5 g/L). The sample was prepared by mixing 2 μL of the matrix solution with 1 μL of analyte solution on the sample holder and the resultant mixture was left to dry in air. Fresh solutions of the matrix and analyte were produced daily. All matrix materials were purchased from Sigma and used without further purification. In both MALDI and chopped beam experiments, a low-resolution time-of-flight spectrum can be observed on the pickup electrode at the center of the trap, which aids in controlling the injection and switching time of the mirror voltages. Hence, a specific range of masses can be stored by carefully selecting the switching time of the entrance mirror relative to the arrival time of the ions.

RESULTS AND DISCUSSION

For small molecular and atomic ions at kiloelectronvolt energies, the major loss process in the trap is collisions with the residual gas, resulting in neutralization and scattering of the stored ions. Neutralized particles leave the trap and about a quarter (assuming a detection efficiency of 0.5) can be detected on the MCP detector behind the mirror at the exit side of the trap (the other half escape in the opposite direction). By counting the total number of neutrals that arrive at the MCP detector after injection of ions, the total number of ions that have been trapped can be determined. This allows studying the trapping stability experimentally as a function of the Einzel lens voltage V_z of the ion mirrors. A relationship between V_z and the focal length f_1 is obtained by simulations using Simion.³⁸ This allows plotting the trapping stability as a function of the inverse of the focal length.³³ This has been done for argon ions at a kinetic energy of 4.2 keV, which have been injected into the trap in bunches of 2- μs length. In Figure 3, the total number of neutrals leaving the trap as a

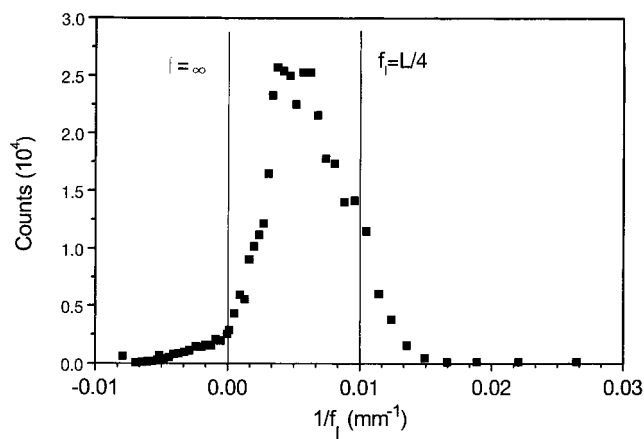


Figure 3. Trapping stability as a function of the Einzel lens potential V_z . The solid lines indicate the theoretical limits for trapping according to eq 1.

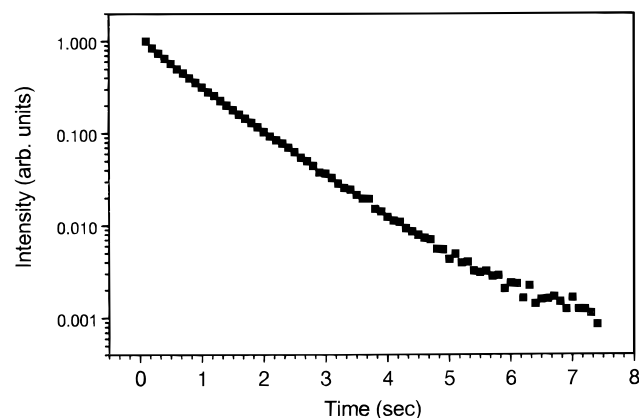


Figure 4. Count rate of neutral particles measured by the MCP for argon ions stored in the trap at 4.2 keV ($p = 3 \times 10^{-10}$ Torr).

function of the inverse focal length is shown. The vertical lines give the theoretical stability limits for trapping according to eq 1. The measured stability limits agree well with the theoretical values and shows that the trap indeed functions analogously to an optical resonator.

The count rate of neutrals measured by the MCP is proportional to the number of ions present in the trap at the same time. This allows measuring the storage lifetime in the trap. Such a measurement is shown in Figure 4 for argon ions injected at an energy of 4.2 keV and a background pressure of 3×10^{-10} Torr. A single-slope exponential decay can be observed, and a storage lifetime of 0.95 s was determined. From the lifetime, the effective mean path length of an argon ion in the trap exceeds 100 km. The measured lifetimes were found to be proportional to the residual gas pressure.

Mass spectrometric measurements are performed by injecting short ion bunches and observing the signal on the pickup electrode. Since an image charge pulse is detected on every pass through the pickup, independent of its direction, and since the pickup is halfway between the mirrors, the measured frequency is twice the frequency of a round-trip oscillation. As a first test of the detection and the FT scheme, argon ions of 4.2-keV kinetic energy were stored in the trap. The frequency spectrum is shown in Figure 5, where 500 FT spectra have been averaged and a background spectrum has been subtracted. The peak width of

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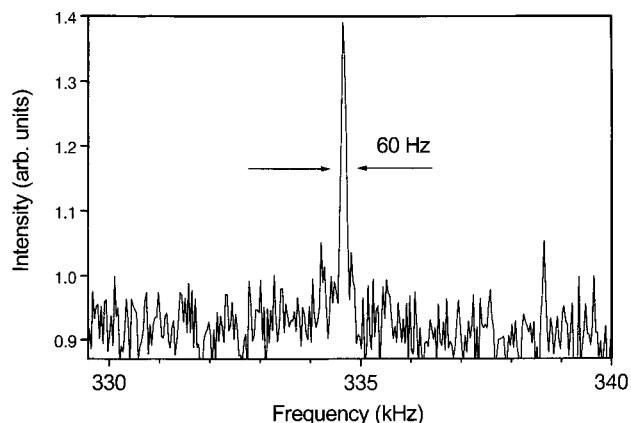


Figure 5. Frequency domain spectrum of trapped argon ions. The fwhm is 60 Hz.

the fundamental is $\Delta f = 60$ Hz and using $R = m/\Delta m = f/2\Delta f$, a mass resolution of $R \approx 2800$ is calculated. The FT spectrum shows higher harmonics of this signal. Mass resolution of $R = 558$ is achieved for a trapped Xe^+ beam at the same kinetic energy.

A short bunch of ions of velocity v and a velocity distribution characterized by Δv , is initially well localized in space between the mirrors. With increasing trapping time, it spreads out until it eventually completely fills the trap. A train of voltage pulses, separated by half the round-trip oscillation time, is observed on the pickup electrode. The width of the velocity distribution translates into a width in the Fourier transform signal. The non sine wave nature of the pickup signal leads to the appearance of higher harmonics in the Fourier spectrum, which are usually not observable in FTICR. It should be noted that interference with smaller masses stored in the trap, at exactly the same frequency as the harmonics, may complicate the mass spectrum. For ideally hard reflecting mirrors, i.e., when the energy of the particles is constant in the mirror region, the energy distribution can be estimated directly from the energy distribution of the ion source ($E/\Delta E \approx 4000$), leading to a mass resolution of $R = 4000$. This is in reasonable agreement with the measured resolution, considering that the actual width in energy distribution might be larger than the nominal value. The width of the velocity distribution is the dominant factor on the mass resolution in the ion trap, as in TOF-MS, so one has to minimize the velocity spread of the source and use compensating mirrors to minimize dispersion within the trap.

Following the experiments with Ar^+ and Xe^+ , ions from the MALDI source were injected. The timing for switching on of the trap mirrors was chosen to trap PEG oligomers of different masses. During the MALDI ionization process using DHB as matrix material, PEG oligomers form sodium adduct ions PEG_nNa^+ .³⁹ A frequency spectrum of PEG_nNa^+ ($n = 7-13$) is shown in Figure 6. The ions were accelerated to 3.15 keV without extraction delay. For PEG_9Na^+ (average $m/z = 437$) a fundamental frequency of 87.1 kHz and a peak width of 250 Hz are measured, resulting in a mass resolution of $R \approx 174$. The spectrum also shows the second and third harmonics of the signal and a small peak, marked by an asterisk, which was not completely removed by background subtraction. Mass spectra were also measured for the peptide bradykinin ($m/z = 1060$). The spectrum in Figure 7 shows a peak at 56 kHz corresponding to the protonated peptide

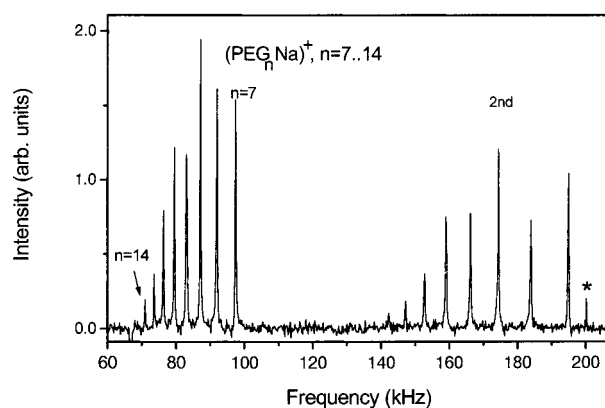


Figure 6. First and second harmonics of the frequency domain spectrum of trapped PEG_nNa^+ ions.

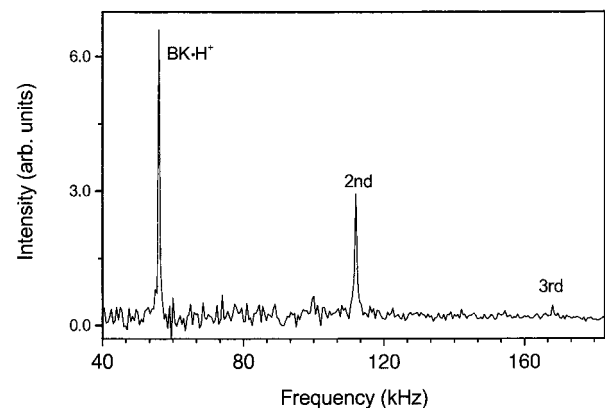


Figure 7. First three harmonics of the frequency domain spectrum of trapped bradykinin ions.

and its second and third harmonics. No doubly charged BK could be observed. For the protonated bradykinin, a mass resolution of $R \approx 130$ is obtained.

As pointed out above, higher mass resolution can be obtained by reducing the velocity spread of the particle bunches before injection. In our experiments, we employ the delayed extraction technique to reduce the velocity spread of the particle bunches. We point to a difference between application of DE in TOF instruments and DE used here. In MALDI-TOF, DE is used to minimize the dependence of flight time on the initial ion velocity, so that all ions of a given mass reach the detector at the same time. Here, DE is used to reduce the velocity spread so that, for a bunch of ions of a given mass, dispersion in the trap is avoided. In Figure 8, an enlargement of the mass spectrum of PEG_nNa^+ from Figure 6 is shown, together with a mass spectrum taken under DE conditions (500-ns HV delay time). The resolution is improved in the DE spectrum ($R \approx 310$), and a peak shift to slightly lower frequencies can be observed in the FT spectrum. Equivalent effects—resolution enhancement and shifts to longer flight times—are observed in DE MALDI in TOF instruments. The operation of DE shows that (1) the velocity distribution from the MALDI source limits the resolution in the FT spectrum (Figure 6) and (2) energy compensation methods as they are used in TOF mass spectrometry are applicable for improving the mass resolution in the ion beam trap. The mass resolution obtained using DE is still comparatively low, which is likely due to space charge effects in the source, which are not sufficiently corrected by DE.

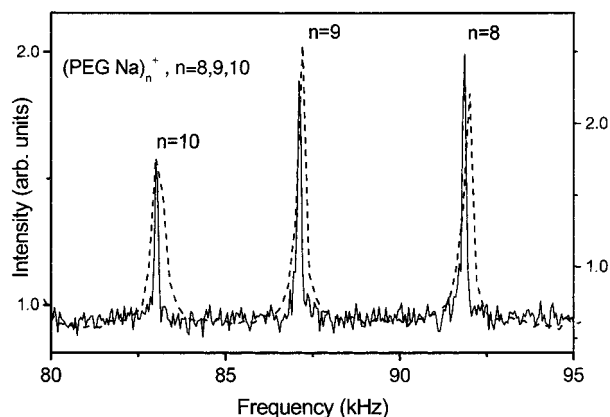


Figure 8. Comparison of the frequency domain spectra of trapped PEG_nNa^+ ions for delayed (solid line) and nondelayed (dashed line) extraction. For clarity, only three masses of the first harmonic are shown. The intensity for delayed (nondelayed) extraction is given on the left (right) intensity axis.

We expect very high resolution for large molecules by applying DE and running the ion mirrors in compensating mode. Other factors that limit the mass resolution in TOF instruments, such as trigger jitter, laser pulse duration, or time response of the MCP detector,¹⁵ are irrelevant in this ion beam trap using Fourier techniques. Technical improvements, such as more ripple-free high-voltage supplies will further improve resolution. Energy compensation methods in effect avoid the dispersion of ion bunches in the trap and will therefore increase the sensitivity of the instrument, together with optimized charge detection. These technical improvements are now being carried out in our laboratory, and results will be reported in a future publication.

CONCLUSIONS

A general purpose mass spectrometer based on an electrostatic ion beam trap has been described. It can operate as an ion trap for a broad range of masses simultaneously or as a Fourier

transform time-of-flight mass spectrometer. The ion flight path length is in the range of kilometers and is only limited by the residual gas pressure. The nondestructive, mass-independent charge detection enables operation at low energies and is particularly useful for the mass spectrometry of large molecules. For medium-sized molecules, the resolution obtained is comparable with standard TOF mass spectrometry in similar instruments. Resolution and sensitivity will be improved by using energy-compensating ion mirrors and more sensitive detection electronics. Further numerical simulations will be done to evaluate inherent resolution limiting factors such as the spatial beam width. Possible experiments can exploit both the trapping and the mass spectrometric capabilities of the ion beam trap. Lifetime measurements can be performed on time scales of tens or even hundreds of milliseconds, which are not accessible in TOF instruments, and both unimolecular and collision processes with the residual gas can be studied. The study of collision processes is particularly interesting for large biological molecules, since their structure is of interest for their functional properties.⁴⁰ We also plan to introduce Schottky mass spectrometry to TOF-MS, a technique so far employed only in particle storage rings.^{29,30}

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