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Abstract

We have measured the radial velocity distributions of protonated intact dynorphin 1-13 ions, produced during matrix-assisted laser desorption/ionization (MALDI) (close to the threshold for ion production), and of the protonated dimer of the MALDI matrix α-cyano-4-hydroxycinnamic acid. For both ion species, the radial component of the velocity was found to be considerably smaller than the axial component, implying angular distributions for both matrix and polypeptide ions that are strongly forward peaked. This extreme forward peaking ($\cos^{28}\theta$ for the peptide ions and $\cos^{12}\theta$ for the matrix ions) lends support to the earlier proposals of a jet expansion model for MALDI. Our observation that the peptide ions exhibit a considerably higher degree of forward peaking than ions arising from the matrix awaits detailed explanation. The present results should prove useful for the design of highly efficient MALDI mass spectrometers. © 1997 Elsevier Science B.V.

Keywords: Matrix-assisted laser desorption/ionization; Molecular ion; Radial velocity distribution

1. Introduction

During the late 1980s, Karas and Hillenkamp [1] discovered a powerful new method for putting intact massive biomolecules into the gas phase and ionizing them for subsequent mass spectrometric analysis. This versatile and sensitive technique, termed matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS), involves directing a short-duration (1-10 ns) pulse of laser light onto a specially prepared sample in the vacuum of a mass spectrometer [2,3]. The sample is typically prepared by mixing, in solution, a small quantity of the biomolecule of interest with a large molar excess of a ''matrix'' compound [2–6], applying a small volume of the resulting solution to the sample probe of a mass spectrometer, followed by drying to give a microcrystalline solid layer. Under appropriate conditions [3], the biomolecules of interest are incorporated into the matrix crystals [5,7,8]. On irradiation with laser light having a wavelength that is strongly absorbed by the matrix crystals, the matrix and incorporated biomolecules undergo a phase transition from the solid to the gas phase, and a fraction of these molecules are ionized.

Although a number of models for the processes underlying the phase transition and ionization have been proposed (reviewed in Ref. [9]), insufficient experimental data have been obtained to assess definitively their relative merits. What is certain is that, after irradiation of the matrix/sample mixture with UV

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wavelength photons ($\lambda \leq 0.4$ μm), a fraction of the initial electronic excitation energy is converted into vibrational excitation and translational motion of the matrix molecules. Although the processes governing this energy conversion remain to be elucidated, some details may not be critical for either the phase transition or the ionization process [9], since IR wavelength light ($\lambda = 2.9$ μm) is as effective as UV light in inducing MALDI of biomolecules [10].

Beavis and Chait [11] have previously determined the velocity distribution of intact protonated polypeptide ions (molecular mass, 1000–15 600 Da) emitted normal to the sample surface ("axial" in the time-of-flight analyser nomenclature) during MALDI, and found the most probable axial velocity to be approximately 750 m s^{-1}, regardless of the molecular mass. Verentchikov et al. [12] have confirmed this lack of dependence of the axial velocity on the molecular mass over a broader range of polypeptide masses, although they determined a somewhat lower axial velocity (approximately 500 m s^{-1}). These results show that the translational energy distributions are mass dependent and scale approximately linearly with the molecular mass, leading to the suggestion [11] that an explanation for the observed axial velocity distributions involves a model based on the formation of a supersonic jet expansion produced by laser irradiation [9,13–18]. In this model, a layer of the matrix is excited by the laser light, causing a rapid phase transition of the matrix molecules from a solid to a high-pressure fluid. This fluid is then free to expand adiabatically into the vacuum, forming a supersonic jet, which carries large molecules contained within the expanding jet into the gas phase. The large molecules are accelerated by the rapidly expanding matrix gas, resulting in similar mean velocities for all molecules entrained in the jet.

In this paper, we extend our earlier work by measuring the component of the velocity distribution of the matrix and polypeptide ions parallel to the sample surface, i.e. the "radial" velocity distribution. These new measurements, performed at irradiances close to the threshold for ion production, yield angular distributions for both matrix and polypeptide ions that are strongly forward peaked. We compare our results with the radial velocity distributions previously determined by Ens et al. [19] and the angular distributions previously obtained by Spengler and coworkers [20,21] and discuss the

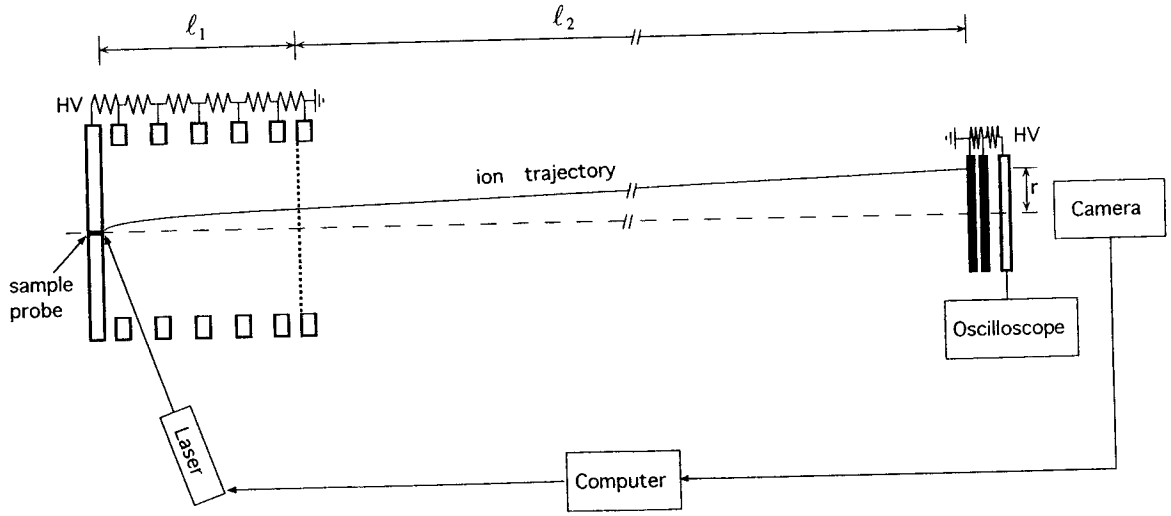

Fig. 1. Experimental set-up for the radial velocity distribution measurements ($l_1 = 4.3$ cm, $l_2 = 35.6$ cm). The trajectory of a typical ion ejected from the sample surface is shown.

implications of our findings for the design of mass spectrometers using MALDI ion sources and for the theoretical treatment of the MALDI process.

2. Experimental details

A schematic representation of the instrument used to measure the radial velocity distributions is shown in Fig. 1. It is essentially a linear MALDI time-of-flight mass spectrometer [22]. Ions generated by laser irradiation of the sample surface are accelerated in a uniform electric field region (l_1), traverse a field free region (l_2) and impact on an ion detector. The detector, consisting of a chevron dual microchannel plate and a phosphor screen (model 3025-FM, Galileo Electro-Optics Corp., MA), allows both the time-of-flight spectrum to be measured and individual impacting ions to be visualized as bright dots on the phosphor screen. The time-of-flight spectrum serves to monitor the identity of the ions hitting the detector. Using an accurate digital delay generator (model DG535, Stanford Research Systems, Palo Alto, CA), triggered to start by the laser pulse, the detector can be gated "on" by a short-duration (as short as 600 ns) high-voltage pulse (model AV-HVX-1000A high-voltage pulser, Avtech Electrosystem Ltd., Ont., Canada) timed to allow detection and visualization of a single selected ion species. The active imaging area of the detector is a disc with a diameter of 2.5 cm. The ion image from each laser pulse is recorded by a video camera (model TM-74SE, Pulnix America Inc., CA) and a frame grabber (OFG, Imaging Technology Inc., MA), synchronized with the laser pulse, whereupon the image (640 × 480 pixels) is transferred to a personal computer (IBM compatible 486, Gateway, SD) for subsequent analysis. The synchronization and the image recording process are controlled by a custom C language program incorporating a library of imaging processing subroutines (ITEX-OFG, Imaging Technology Inc., MA) written for use with the frame grabber.

The electric acceleration field was designed to be highly uniform and devoid of radial components that could obscure the intrinsic radial velocity component of the ions which emanate from the sample surface. This was accomplished by distributing appropriate potentials on a series of ring electrodes in the spatial configuration shown in Fig. 2, using the resistive potential divider indicated. The theoretical uniformity of the field in the central axis region is demonstrated by the extreme flatness of the equipotential lines simulated with the ray tracing program SIMION [23].

The laser (Lumonics HY400 Nd:YAG operated in the Q-switched mode to give 10 ns duration pulses, frequency tripled to $\lambda = 0.355$ μm) was focused onto the sample with an $f = 30$ cm lens at an angle of incidence of 70° to give an ellipse with minor and major axes of 100 μm and 300 μm respectively.

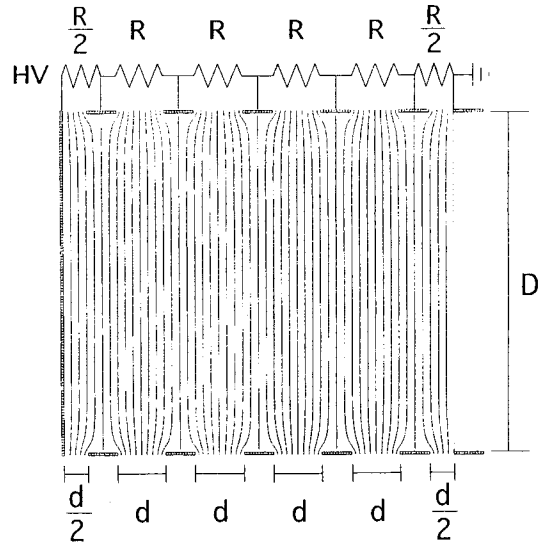

Fig. 2. Detail of the acceleration region showing the spatial and electrical configuration of the acceleration electrodes (d = 0.54 cm; thickness of the ring electrodes, 0.32 cm; D = 3.82 cm; R = 100 MΩ). The grid has 70 wires per inch. Also shown are the equipotential lines calculated using the SIMION program [23], assuming cylindrical symmetry.

Samples were prepared for the measurements in three different ways.

1. Thin layer preparations of the cationic dye brilliant green were prepared by placing a small volume (approximately 0.5 μl) of a dilute methanolic solution of the dye onto the flat surface of a stainless steel probe (diameter, 2 mm; electropolished to a mirror finish) and allowing the solvent to evaporate.
2. Thin layer preparations of matrix and matrix containing polypeptide were prepared by a method previously described by Xiang and Beavis [24]. A small volume (approximately 0.5 μl) of a saturated matrix solution (acetonitrile/0.1% aqueous trifluoroacetic acid (1 : 2, v/v)) was applied to the flat surface of the stainless steel probe, allowed to dry and then rubbed with a Kimwipe tissue to crush the crystals on the metal surface. During this process, most of the matrix material is removed and an extremely thin layer of flat crushed crystal residue is left on the surface. This layer serves to nucleate a thin contiguous layer of sample when a solution (volume, 0.5 μl) of saturated matrix (5 μg μl^{-1}) or saturated matrix containing polypeptide (approximately 1 pmol) is applied to this specially prepared surface. The resulting thickness of the final sample layer was estimated to be approximately 0.5 μm.
3. Large (5 mm × 1.2 mm × 0.8 mm) sinapic acid crystals were grown from saturated matrix solutions (acetonitrile/0.1% aqueous trifluoroacetic acid (1 : 2, v/v)) over periods of days to weeks [7]. Thin (approximately 0.5 mm) slices of these crystals were prepared by cleavage with a sharp object (scalpel tip) along the readily cleavable $(10\bar{3})$ crystal plane [7]. These newly cleaved crystal faces were shown to be flat on a molecular scale by atomic force microscopy (Nanoscope AFM, Digital Instruments, Santa Barbara, CA). The cleaved crystal slice was mounted with its $(10\bar{3})$ face against the flat face of the stainless steel probe using a small quantity of Apiezon L high-vacuum grease (M & I Material Ltd., Manchester, UK).

To deduce the angular distributions of the ions emitted from the sample probe from the present radial velocity distribution measurements, it was necessary to determine the axial velocity distributions for the ions of interest. These axial velocity distributions were measured using a previously described experimental set-up [11], slightly modified by the use of a finer grid (750 wires per inch vs. 70 wires per inch used in the earlier experiment; Buckbee-Mears Co., St. Paul, MN) to minimize field penetration effects (apparatus not shown). For each ion species, spectra were taken at a series of acceleration voltages between 5 and 20 kV, and the most probable axial velocity was determined by linear extrapolation to zero voltage to correct for residual field penetration effects. The most probable axial velocities and their estimated errors are given in Table 1.

The radial velocity measurements were performed at laser fluences very close to the threshold for ion production, i.e. the number of ions detected per laser pulse was kept to less than

Table 1
Axial velocity

	MM (Da)	Axial velocity (m s^{-1})
Dynorphin 1-13[a]	1604	660 ± 60
Dimer of α-cyano-4-hydroxycinnamic acid[a]	378	850 ± 100
Sinapic acid[b]	225	1050 ± 100
Brilliant green	386	615 ± 50

[a] Mixture of dynorphin 1-13 and the matrix α-cyano-4-hydroxycinnamic acid [6] was used for the measurements. [b]Sample of neat sinapic acid [4].

100. To derive the radial velocities of the emitted ions, the positions of the ions striking the detector were measured by analysing the acquired images using IMAGEPRO PLUS software (version 1.2 for DOS, Media Cybernetics, MD). The coordinates of approximately 1000 ion dots were obtained for each experimental setting. The centroid of these dot coordinates was determined and defined as the position at which ions with zero radial velocity strike the detector. Fig. 3 shows an accumulation of 1169 ion dots from 126 separate ion images (laser pulses), measured for the cationic dye brilliant green (molecular mass (MM) = 386 Da) at an acceleration voltage of 5 kV, with the origin of the coordinates defined as the centroid. The dimension scale (pixel mm^{-1}) was obtained from an image of graph paper aligned in both x and y dimensions on the edge of the phosphor screen. As illustrated in Fig. 1, the radial distance (r) of each ion dot to the centroid is the radial displacement that the ion experiences during the time period from laser ablation to ion detection. The corresponding radial velocity is

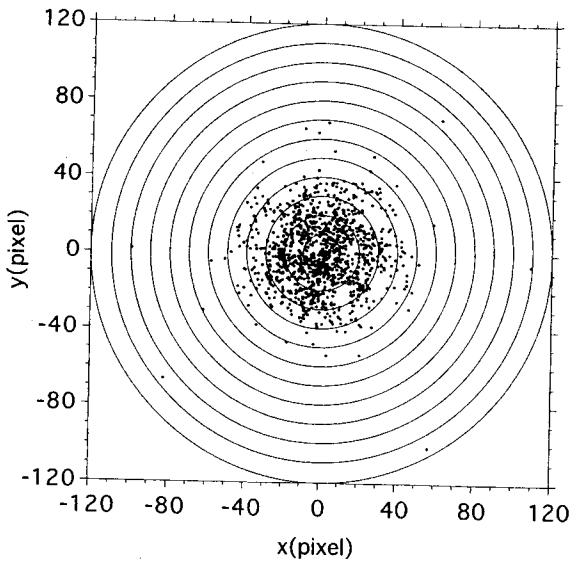

Fig. 3. Coordinates of fluorescent dots produced by the impact of brilliant green ions (5 kV acceleration voltage) on the position sensitive detector. There are a total of 1169 dots recorded from 126 laser pulses, i.e. 126 separate ion images. The origin of the coordinates is defined as the centroid, and the dimension scale is 12.4 pixel mm^{-1}. The circular bins indicated are 10 pixels wide.

then derived from the relation

$$v_r = \sqrt{\frac{2eV}{m}} \frac{r}{2l_1 + l_2}$$

where v_r is the radial velocity, r is the radial displacement, l_1 is the length of the acceleration region, l_2 is the length of the field free region, V is the total acceleration voltage and m and e are the mass and charge of the ion. Assuming that the radial velocity distribution is cylindrically symmetrical with respect to the sample surface normal, the radial velocity distribution $f(v_r)$ can be obtained through the relationship that $f(v_r)v_r dv_r$ is proportional to the number of ions in a ring bin, with the normalization condition $\int_0^\infty f(v_r)2\pi v_r dv_r = 1$. The ion dot distribution was distorted slightly by a lens effect from the small holes in the grid positioned at the exit of the acceleration region giving rise to fine-scale inhomogeneities in the ion dot distribution (Fig. 3). The bin width (10–20 pixels) was chosen to average over (smooth) these fine-scale inhomogeneities. Given the axial velocity v_a, the ion ejection angle with respect to the sample surface normal is

$$\theta = \arctan \frac{v_r}{v_a}$$

The angular distribution $f(\theta)$ can be derived from the relationship that $f(\theta) \sin\theta \, d\theta$ is proportional to the number of ions in a ring bin, with the normalization condition $\int_0^{\pi/2} f(\theta)2\pi \sin\theta \, d\theta = 1$.

3. Results

To test for the presence of stray radial or non-axial electric fields in the ion acceleration region, we determined the radial velocity distribution of a thin microcrystalline layer of the cationic dye brilliant green (see Section 2) at different acceleration voltages. The radial velocity distributions obtained at 5 kV and 10 kV are compared in Fig. 4, where it can be seen that the distributions are almost the same, within the experimental

error of the measurement. We conclude from these measurements that non-axial components of the acceleration field (in the region traversed by ions which emanate from the sample surface) are not of sufficient magnitude to obscure the intrinsic radial velocity components of these ions.

The MALDI mass spectrum of a thin microcrystalline layer of α-cyano-4-hydroxycinnamic acid (4hcca) matrix containing the peptide dynorphin 1-13 (see Section 2) is dominated by the protonated intact peptide ion and a series of peaks arising from the matrix, including $(4hcca + H)^+$, $(4hcca-18+H)^+$ and $(2\{4hcca\}+H)^+$ (data not shown). Fig. 5 shows the radial velocity distribution of protonated dynorphin 1-13 and the protonated 4hcca dimer measured from the same sample. The dimer was chosen over the monomer in these measurements because it was more readily resolved from adjacent interfering peaks by high-voltage pulsing of the detector (see Section 2). At half-height, the radial velocity distributions of protonated dynorphin 1-13 and protonated 4hcca dimer have widths of 140 ± 15 m s^{-1} and 250 ± 30 m s^{-1} respectively and most probable axial velocities of 660 ± 60 m s^{-1} and 850 ± 100 m s^{-1} respectively (Table 1), showing that both ion species are ejected from the solid sample surface in a highly forward-peaked manner. The extreme forward peaking can be seen more graphically when we plot the angular distributions using the present radial and axial velocity data (Fig. 6). The angular distribution for protonated dynorphin 1-13 can be fitted well by a $\cos^{28}\theta$ distribution, while that for the protonated 4hcca dimer is best fitted by a $\cos^{12}\theta$ distribution. Thus we observe that the higher mass peptide species is significantly more forward peaked than the matrix ions.

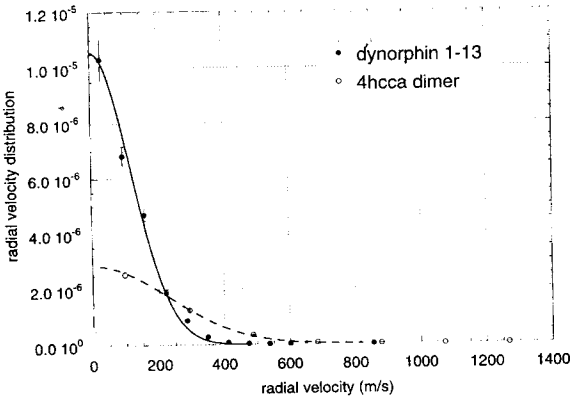

Fig. 5. Radial velocity distributions of protonated dynorphin 1-13 and protonated 4hcca matrix measured from the same sample at 10 kV acceleration voltage. Lines through the data points were generated using Maxwellian distributions (see text).

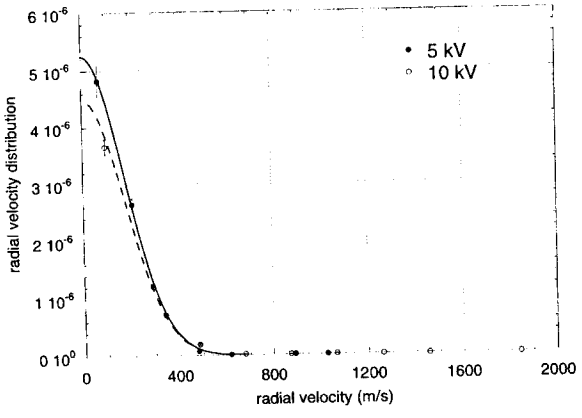

Fig. 4. Radial velocity distributions of brilliant green cations obtained at two different acceleration voltages: ●, 5 kV; ○, 10 kV. Lines through the data points were generated using Maxwellian distributions (see text).

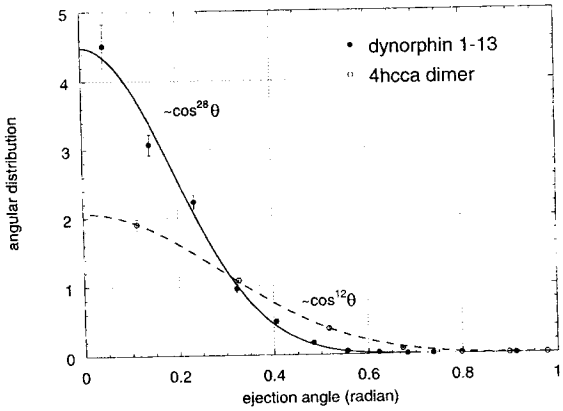

Fig. 6. Angular distributions of protonated dynorphin 1-13 and protonated 4hcca matrix measured from the same sample at 10 kV acceleration voltage. The power of the $\cos^n\theta$ fit is indicated.

Although the sample layers used in the present experiments were relatively thin (estimated to be approximately 0.5 μm), they were certainly not flat on the microscopic scale, but were composed of a large collection of microcrystals. In an effort to ascertain the effect of this surface roughness on the angular distributions of the emitted ions, we compared the angular distribution obtained from a thin microcrystalline sample layer with that obtained from the highly flat surface of a cleaved single matrix crystal (Fig. 7). Subsequent to the measurement, the surface of the crystal did not appear to be grossly damaged (by visual light microscopy), presumably because we were working very close to the threshold for ion production (less than 100 ions detected per laser pulse). Fig. 7 shows that the angular distribution from the microcrystalline sample layer was more forward peaked ($\cos^{14}\theta$) than that from the single crystal ($\cos^{9}\theta$).

4. Discussion

The present measurements of the axial velocity distributions of protonated peptide ions produced by MALDI using a matrix of 4hcca are in agreement with our earlier findings for sinapic acid [11], i.e. the matrix ions have a higher mean axial velocity than the peptide ions. As in our earlier work, we do not have a detailed explanation for this apparent "straggling" of the larger peptide molecular ions.

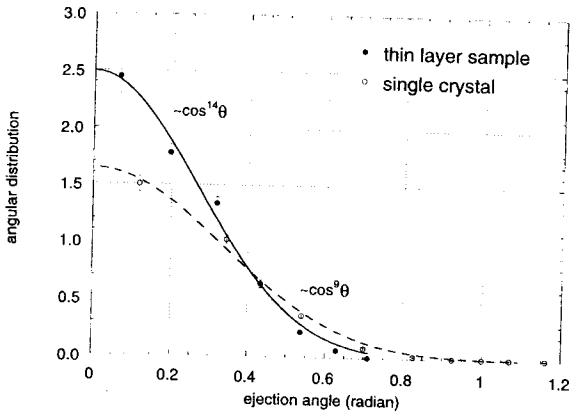

Fig. 7. Angular distributions for protonated sinapic acid ejected by MALDI from a thin layer sample of microcrystals (●) and a cleaved single crystal (○). An axial velocity of 1050 m s^{-1} (determined from the thin microcrystalline sample) was used to calculate both angular distributions. The power of the $\cos^{n}\theta$ fit is indicated.

The extreme forward peaking observed for both matrix and peptide ions lends support for earlier proposals of a jet expansion model for MALDI [11,16,17]. It is noteworthy that the higher mass peptide ions have considerably lower radial velocities than the matrix dimer ions, leading to stronger forward peaking for the peptide ions ($\cos^{28}\theta$) compared with the matrix ions ($\cos^{12}\theta$). This finding may be an indication of the partial equilibration of the temperature of the molecules comprising the expanding plume, and it is of considerable interest to determine whether this trend continues for still higher mass polypeptides. Such experiments are in the planning stage. Although we can fit the velocity distributions very well with a non-equilibrium distribution function incorporating two maxwellian distributions with different perpendicular and parallel temperature parameters [25,26], we introduce the notion of plume temperature with caution because the temperatures obtained from these fits appear to be unrealistically high (above 2000 K).

The angular distribution for protonated sinapic acid ions emitted from the $(10\bar{3})$ face of a microscopically flat single sinapic acid crystal was found to be less forward peaked than that obtained from the thin microcrystalline matrix layer. However, it is likely that the 0.5 mm thick crystal (being a dielectric) undergoes charging during laser irradiation, leading to distortion of the intrinsic angular distribution. It is therefore of interest to repeat these measurements with much thinner crystal slices.

Our present axial and radial velocity distributions are in qualitative agreement with the results of Ens et al. [19] who observed strong forward peaking for insulin ion ejected from sinapic acid. Our inferred angular distributions differ in some

respects from the results previously obtained by Spengler and coworkers [20,21]. In particular, we found no indication of the bimodal ejection of the matrix with slow (less than 1000 m s^{-1}) and fast (approximately 2000 m s^{-1}) axial velocity components, and we observed considerably more forward-peaked angular distributions for the matrix ions ($\cos^{12}\theta$ for the protonated dimer of 4hcca (present work) and $\cos^{14}\theta$ for the protonated monomer of sinapic acid (present work) vs. $\cos^{3.6}\theta$ for the protonated monomer of 2,5-dihydroxybenzoic acid [20]). It is difficult to assess the origin of these differences because the experimental conditions were very different in the two experiments. Specifically, the present experiment used different matrices, worked closer to the threshold for ion production, used higher angular resolution and obtained the angular distributions in a very different way.

Measurements made at Orsay [27] provide evidence that the emission of peptide and protein ions by MALDI is, on average, directed back towards the direction of the laser. In our present measurements, we have not determined whether or not the emission is normal to the surface. Rather, we take the centroid of the ion positions as corresponding to the position with zero radial velocity, and determine the angular distribution about this average.

The magnitude of the radial component of the velocity distribution has important implications for the design of certain types of mass spectrometer which use MALDI ion sources. In time-of-flight instruments, without ion focusing or guiding elements, the non-zero component of the radial velocity will cause the ion beam to expand en route to the detector and the ion beam may grow considerably larger than the detector face leading to a loss in efficiency. This problem is severe for analysers with long flight paths, especially instruments fitted with long electrostatic mirrors (reflectrons). In such cases, an electrostatic lens and/or an ion guide [28] may prove useful in maintaining an adequately small beam area at the detector. The size of the radial velocity component also has important implications for the design of instruments which use low extraction fields in the ion source, including MALDI ion trap mass spectrometers [29], MALDI Fourier transform ion cyclotron resonance mass spectrometers [30] and orthogonal injection MALDI time-of-flight mass spectrometers [31]. In the absence of ion focusing or guiding in the region of the low extraction field, the low-velocity beam may expand sufficiently in size to cause considerable losses prior to entering the mass analyser proper, although the relatively small ejection half-angle (approximately 13°) for the peptide ions mitigates, to some extent, these beam expanding effects. The present results may prove useful in the design of highly efficient MALDI mass spectrometers.

5. Conclusions

We have measured the radial velocity distributions for protonated intact dynorphin 1-13 ions produced during MALDI (close to the threshold for ion production) as well as the protonated dimer of the MALDI matrix α-cyano-4-hydroxycinnamic acid. For both ion species, the radial component of the velocity was found to be considerably smaller than the axial component, implying angular distributions for both matrix and polypeptide ions that are strongly forward peaked. This extreme forward peaking lends support for earlier proposals of a jet expansion model for MALDI. Our observation that the peptide ions exhibit a considerably higher degree of forward peaking than ions arising from the matrix awaits detailed explanation. The present results should prove useful for the design of highly efficient MALDI mass spectrometers.

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