

A deflection system to reduce the interference from post-source decay product ions in photodissociation tandem time-of-flight mass spectrometry

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A deflection system consisting of four deflectors was designed and used to reduce the interference from post-source decay (PSD) product ions in photodissociation (PD) tandem time-of-flight (TOF) mass spectrometry. For simple protonated peptides generated by matrix-assisted laser desorption/ionization, the presence of PSD product ions at the laser irradiation spot was found to noticeably alter the minor peaks in the PD spectra even though the major ones were hardly affected. Other benefits from the use of the deflection system such as the improvement in the resolving power in PSD tandem mass spectra are discussed. Copyright © 2006 John Wiley & Sons, Ltd.

Tandem time-of-flight (TOF) mass spectrometry is widely used to record fragmentation spectra of biomolecular ions generated by matrix-assisted laser desorption/ionization (MALDI).^{1,2} In fact, it is regarded as one of the most powerful techniques to determine the amino acid sequences of peptides.^{3–6}

A MALDI tandem TOF usually consists of the first stage TOF with delayed extraction,^{7,8} and the second stage incorporating a reflectron. An ion gate⁹ is installed at or very near the first time-focus of the instrument to select the precursor ion of interest based on its time of flight. When the ion gate timing is set to transmit a particular precursor ion, its post-source decay (PSD)^{10–14} products also pass the gate. Then, setting the ion gate timing and time-dispersing the PSD product ions using the reflectron result in a PSD spectrum. When the same method is used with collisionally activated dissociation (CAD) in a cell placed near the first time-focus, contamination of the resulting CAD^{15–17} spectrum by PSD becomes inevitable.

Recently, we reported homebuilt tandem TOF mass spectrometers developed for photodissociation (PD) of protonated peptides generated by MALDI.^{18–21} Instead of the usual linear potential reflectron, a reflectron with linear-plus-quadratic (LPQ) potential inside was used in the second stage analyzer. This resulted in tandem mass spectra with decent resolution in the low- m/z region even when the reflectron voltage was kept constant. An ion gate with moderate resolution was used. Tandem mass spectra were recorded without and with the PD laser. The former one

(PSD) was subtracted from the latter one to obtain the photoinduced change, or the photodissociation (PD) spectrum. For protonated peptides with m/z around 1000, PD was found to be quite efficient. For example, PD laser intensity as low as a few tens of μJ per pulse at 193 nm was sufficient to record a decent spectrum.²⁰ Almost complete depletion of the precursor ion signal was achieved as the laser intensity was raised. Also, it was observed that the PD spectra contain lots of information useful for sequence determination of peptides. The results suggest that PD may be developed as a useful routine analytical tool for biomolecules.

A remarkable characteristic of the PD spectra obtained in this laboratory was the selection of a monoisotopomeric precursor ion, which was achieved via ion pulse-laser pulse synchronization.¹⁸ Also, an algorithm was developed to clean up isotopomeric contamination when the time separation between isotopomeric ions at the laser irradiation point was not adequate. Even after the best efforts, however, the ions selected for PD are not entirely the intended precursor ion, but contain its PSD products also. Namely, PSD product ions may undergo PD together with their precursor ion. A striking example is the appearance of negative-going signals, or negative signals, in the PD spectra, some of which may be due to PD of PSD product ions.

Since intensities of PSD product ions are usually much smaller than that of the precursor ion, contamination of the PD spectrum by PD of PSD product ions is not expected to be serious. However, in some applications of PD-tandem TOF mass spectrometry, such as the detailed mechanistic study of the PD process, one may want to be assured that the observed signals arise solely from PD of the precursor ion, not from its PSD products. One may suppress the PSD signals by reducing the laser intensity in MALDI and/or by changing

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the matrix, which can be very difficult or time-consuming sometimes or may decrease the prompt ion signal also. Instead, we have devised a deflection system to reduce the PSD ions at the laser irradiation point. Its performance and utility and degree of contamination of PD spectra by PSD product ions as manifested by its use are presented in this paper.

EXPERIMENTAL

A schematic drawing of the homebuilt MALDI-TOF-PD-TOF instrument equipped with the deflection system is shown in Fig. 1. Since details of the original instrument and the operational method have been reported previously,^{19,20} only a brief account will be provided here.

The original instrument consists of a MALDI source with delayed extraction, a flight tube to time-separate the ions generated in the MALDI source, or prompt ions, an ion gate, and the second stage TOF with an LPQ reflectron. The distance between the source exit and the first time-focus is 680 mm, that between the ion gate to the reflectron entrance is 280 mm, and the multichannel plate detector (MCP, 40/12/8,

Burle, Lancaster, PA, USA) is located very close to the reflectron entrance. Sample is loaded on a stainless steel plate, which is introduced into the source via a vacuum lock and mounted on an *yz*-translational stage. The voltages on the sample plate and the final electrode of the reflectron are 20 and 25 kV, respectively. MALDI is achieved by 337 nm of a 50 Hz N₂ laser (MNL205-C, Lasertechnik Berlin, Berlin, Germany) irradiated at 60° to the surface normal. After a few hundred nanoseconds of delay, 1.8 kV is applied to the sample plate for delayed extraction. A precursor ion is selected by the ion gate which has the resolving power of 30.

An output of 193 nm from an ArF excimer laser (PSX-100, MPB Communications Inc., Montreal, Quebec, Canada) or 266 nm from a Nd:YAG laser (Surelite III-10, Continuum, Santa Clara, CA, USA) was used for PD in this work. To record the laser-on spectrum, a cylindrically focused PD laser was irradiated perpendicularly to the ion beam direction with its pulse synchronized with the lowest *m/z* isotopomer, or the A peak, of the precursor ion. The laser-off spectrum, or the PSD spectrum, was recorded under the same experimental condition without the PD laser. The MCP output was sent to an A/D card (CS82G, Gage Applied Technologies, Montreal, Quebec, Canada), digitized, treated to eliminate electronic noises, and averaged following the method described previously.²⁰

Deflection system

As shown in Fig. 1, the system consists of four identical bipolar deflectors, each consisting of two 50 mm width × 10 mm length rectangular plates separated by 10 mm. The first and fourth deflectors are placed along the ion-optical axis of the instrument while the second and the third are 15 mm off the axis. The distances of the centers of the first to the fourth deflectors from the ion source exit electrode are 125, 315, 385, and 575 mm, respectively. Then, the distance between the end of the final deflector and the first time focus position becomes 100 mm. The first and second deflectors shift the prompt ion trajectory by 15 mm while the third and fourth deflectors restore it back to the original one. This is achieved by applying +1 or −1 kV to the plates as appropriate. Since the translational kinetic energy of a PSD product ion is less than those of the prompt ions, it is deflected more than prompt ions and hence does not arrive at the final detector. PSD product ions formed between the ion source and the first deflector are eliminated mostly by this deflector, those formed between the first and second deflectors by the second, etc. With the potentials turned off, prompt ions move along the original trajectory without any obstruction from the deflection system.

Samples

The peptide sample RLLAPITAY (98% purity) was purchased from Pepton (Daejeon, Korea). Angiotensin II and the matrix, α -cyano-4-hydroxycinnamic acid (CHCA), were purchased from Sigma (St. Louis, MO, USA). All the samples were used without further purification. Matrix solution was prepared daily using acetonitrile and 0.1% trifluoroacetic acid, which was mixed with the peptide solution. The final peptide concentration prepared for the PD experiments was

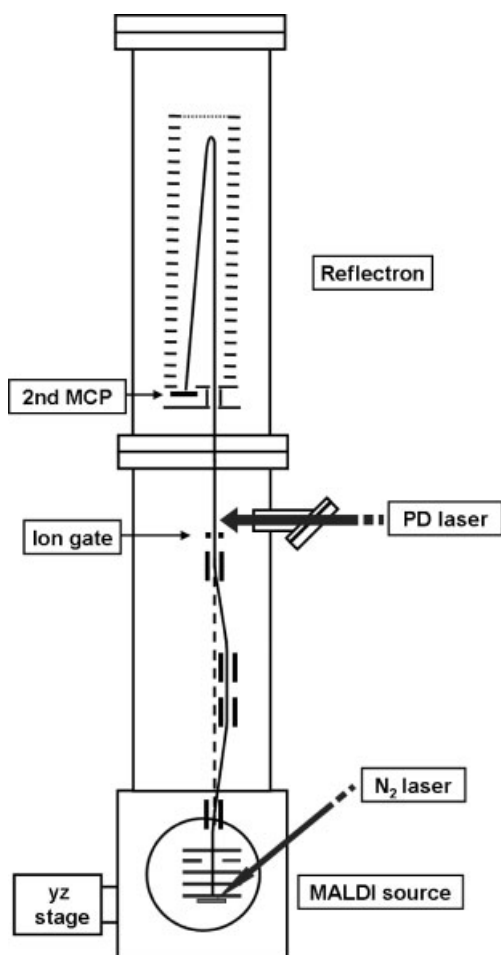


Figure 1. A schematic drawing of the MALDI-TOF-PD-TOF mass spectrometer used in this work. Four parallel plates located between the ion source exit and the PD laser spot are the deflectors. Dashed line shows the ion trajectory when the deflectors are turned off. Details of the instrument and its operation are given elsewhere.²³

around 10 pmol/ μ L and 1 μ L of the solution was loaded on the sample plate.

RESULTS AND DISCUSSION

Calculation of mass-dependent transmission of PSD product ions

SIMION²² calculation was performed to estimate the transmission of PSD product ions through the deflection system. Ions generated by MALDI were assumed to have a velocity distribution in the range 500–1000 ms⁻¹ and be emitted with an even angular distribution up to 60° to the surface normal. For PSD occurring before the first deflector, product ions with m/z less than 85% of the precursor ion m/z were completely cut off by the deflection system. The deflection system was found to be even more selective for PSD occurring between the first and fourth deflectors, product ions with 95% m/z having been cut off.

Ordinary MALDI spectra

We first checked experimentally the influence of the deflection system on MALDI spectra. It was found that the spectra recorded with the deflectors off and on looked nearly identical except for the absolute flight times, those in the latter ones being longer than those in the former ones by 15 ns regardless of m/z . Hence, the mass scale calibration established with the former ones could be used for the latter ones with a minor change. Peak intensities were not affected

either. More importantly, the width of each peak, namely the resolution, was unaffected by the deflection system.

PSD (laser-off) spectra

The PSD spectra of protonated RLLAPITAY (m/z 1017.6) recorded with the deflectors off and on are shown in Figs. 2(a) and (b), respectively. The peak intensities in these spectra have been normalized to those of the precursor ion in each spectrum. The intensity of each peak in the deflector-on spectrum is smaller than the corresponding peak in the deflector-off spectrum, as expected. Taking the prominent y_5 peak at m/z 563.9 as an example, its peak area in the deflector-on spectrum is 48% of the same peak in the deflector-off spectrum. Length of the entire field-free region is 960 mm while the distance between the end of the final deflector and the reflectron entrance is 380 mm. Then, assuming that PSD occurs with the same probability over the entire region, 40% of it is expected to occur after the final deflector. Namely, the observed PSD intensity is a little larger than estimated simply with the geometrical parameters. According to our more elaborate SIMION calculations, it is likely that some of this discrepancy is due to the difference in transmission of PSD product ions, those formed after the deflection system being transmitted better than those formed before. Also to be noted in Fig. 2 is that the relative heights of the strong backgrounds appearing at high- m/z range all the way up to the precursor ion position are nearly the same in the two spectra. These are mostly the chemical noises due to dissociations occurring inside the reflectron. Elimination of some of the PSD product

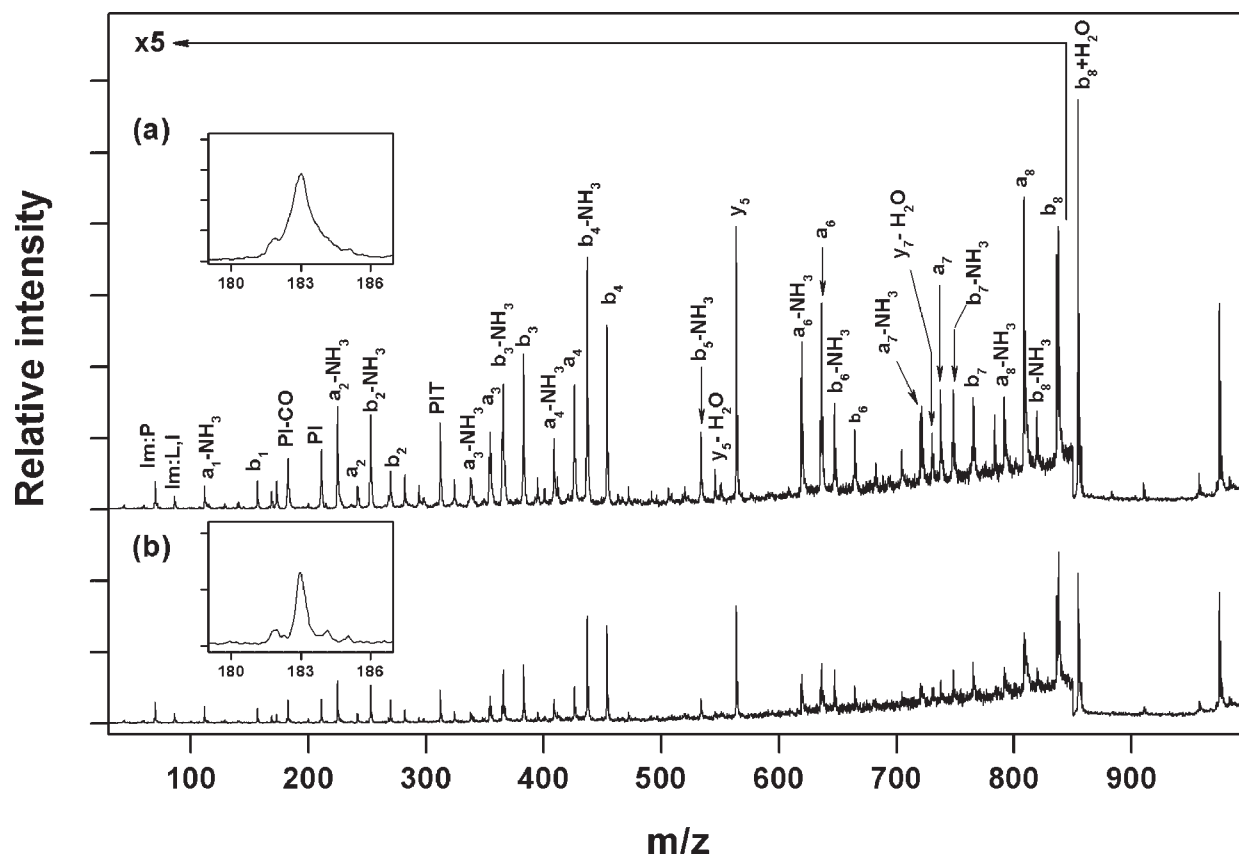


Figure 2. PSD spectra of protonated RLLAPITAY (m/z 1017.6) recorded with the deflectors (a) off and (b) on, normalized to the precursor ion intensity in each spectrum.

ions by the deflection system is not expected to affect the intensity of this background much, as observed.

It is seen in Fig. 2 that some peaks are reduced substantially more than the y_5 peak by the deflection system. For example, the a_6 peak at m/z 636.6 is reduced by as much as 65% as the deflectors are turned on. Substantial intensity reduction is observed for other a_n peaks also such as a_2 (242.3), a_3 (355.1), a_4 (426.1), a_7 (737.7), and a_8 (808.7). In addition, $a_3\text{-NH}_3$ (338.1), $a_4\text{-NH}_3$ (409.1), $a_6\text{-NH}_3$ (619.6), $a_7\text{-NH}_3$ (720.6), $a_8\text{-NH}_3$ (791.4), $b_5\text{-NH}_3$ (534.1), $b_8\text{-NH}_3$ (819.6), $y_5\text{-H}_2\text{O}$ (545.9) and $y_7\text{-H}_2\text{O}$ (730.6) are substantially reduced. This observation can be explained once it is assumed that all of these are formed consecutively. For example, when the deflectors are turned off, b_n ions generated in the front part of the field-free region are precursors to a_n and $b_n\text{-NH}_3$ ions and contribute to the formation of the latter ions in the back part of the region. When the deflectors are turned on, b_n ions formed in the front part are eliminated, leaving only those formed in the back part as the precursor ions to a_n and $b_n\text{-NH}_3$ ions. As a result, a_n and $b_n\text{-NH}_3$ intensities would decrease more than that of b_n .

As has been mentioned already, the resolution for the precursor ion peak is the same regardless of the use of the deflection system. Those for the product ions, however, improve with the use of the deflection system. This is especially conspicuous in the low- m/z region as demonstrated in the insets of Fig. 2 which show the magnified spectral profiles near the PI-CO (m/z 182.8) peak. Explanation for the improvement in the product ion resolution in the deflector-on spectrum is as follows. The instrument is tuned for the best resolution of prompt ion peaks. Namely, a prompt ion time-focused at the first time-focus position is time-focused again at the second time-focus position where a detector is located. Time focusing of a PSD product at the detector position is less than perfect even though addition of the quadratic term in the reflectron potential improves the resolution for the product ions.¹⁹ There is an additional broadening in the product ion time of flight, however, which arises from the kinetic energy release^{23,24} in dissociation. As dissociation occurs further away from the first time-focus, the product ion time of flight differs more from that formed at the first time-focus due to this kinetic energy release. The product ions generated far from the first time-focus are eliminated by the present deflection system. Then, improved resolution in the deflector-on PSD spectrum is not surprising because only those ions formed near the first time-focus or at short distance thereafter are detected. Explanations for the spectral changes upon application of the deflector potentials presented so far suggest that the present deflection system is working properly as intended.

Laser-on spectra

Even though the intensity of a PSD peak in a deflector-on spectrum is as large as 48% of that in a deflector-off spectrum, this does not mean that 48% of the PSD product ions remain at the first time-focus when the deflectors are on. Measuring from the first time-focus point, the source exit and the end of the final deflector are located at 680 and 100 mm, respectively. Assuming the same PSD probability along the

length, the intensity of a PSD peak at the first time-focus point with the deflectors on will be approximately 15% of the corresponding deflector-off intensity. Namely, the contribution from PD of the PSD product ions will be reduced substantially as the deflector voltages are turned on.

The laser-on spectra at 193 nm for the protonated RLLAPITAY recorded with the deflectors off and on are shown in Figs. 3(a) and 3(b), respectively. Even though the two spectra look quite similar as expected, some differences can be readily noticed. First of all, relative intensities of the corresponding peaks in the two spectra are generally different, sometimes conspicuously as exemplified by the a_5 (523.1)/ y_5 (563.9) pair. This can be easily explained by referring to the stronger y_5 signal in the deflector-off PSD spectrum. To show minor but probably more significant differences, magnified portions of the laser-on spectra in the m/z 405–440 range are shown in Fig. 4. It is to be noted that the main peaks in the clusters, which are due to photofragments, have similar widths at the half heights regardless of the use of the deflectors. Upon further magnification, however, one finds that the widths at lower heights are wider when the deflectors were not used. This is due to the presence of PSD peaks with larger widths which have been generated in the earlier part of the field-free region. Also to be noted is that some shoulder peaks in the deflector-off spectrum are absent in the deflector-on spectrum. In fact, more minor peaks are observed in the deflector-off spectrum than in the deflector-on spectrum, some of which may arise due to dissociation of PSD peaks. Previously, we developed an algorithm to reduce the laser-off and laser-on spectra into bar graph forms by fitting each peak into a Gaussian function. A difficulty there was in treating a cluster of peaks which were not sufficiently resolved. A slight improvement in resolution achieved here with the use of the deflectors is sufficient to handle such cases.

PD spectra

The 193 nm PD spectra of the protonated RLLAPITAY with the deflectors off and on obtained by subtracting the laser-off (Fig. 2) spectra from the corresponding laser-on (Fig. 3) spectra are shown in Fig. 5. It is to be mentioned again that a peak in the PD spectrum can appear with negative intensity when its intensity in the laser-on spectrum is weaker than in the laser-off (PSD) spectrum. With the contributions from PSD subtracted, the relative intensities of the corresponding major peaks in the deflector-off and -on spectra have become quite similar, unlike in the laser-on spectra (Fig. 3). Regardless, some differences can be noted. Firstly, negative peaks are noticeably subdued in the deflector-on spectrum than in the deflector-off spectrum, indicating less contribution from PD of PSD product ions. As another demonstration of this effect, the 266 nm PD spectra of the protonated angiotensin II ([DRVYIHPF+H]⁺, m/z 1046.5) recorded with the deflector potentials off and on are shown in Fig. 6. Substantial decrease in the negative signal intensities in the deflector-on spectrum is also evident. A noticeable example is the intensity of $b_7 + \text{H}_2\text{O}$ (899.7) which goes from negative to positive when the deflector potentials are applied. In this case, PD of the precursor ion generates this fragment ion while the fragment ion itself is depleted by PD. Decrease in

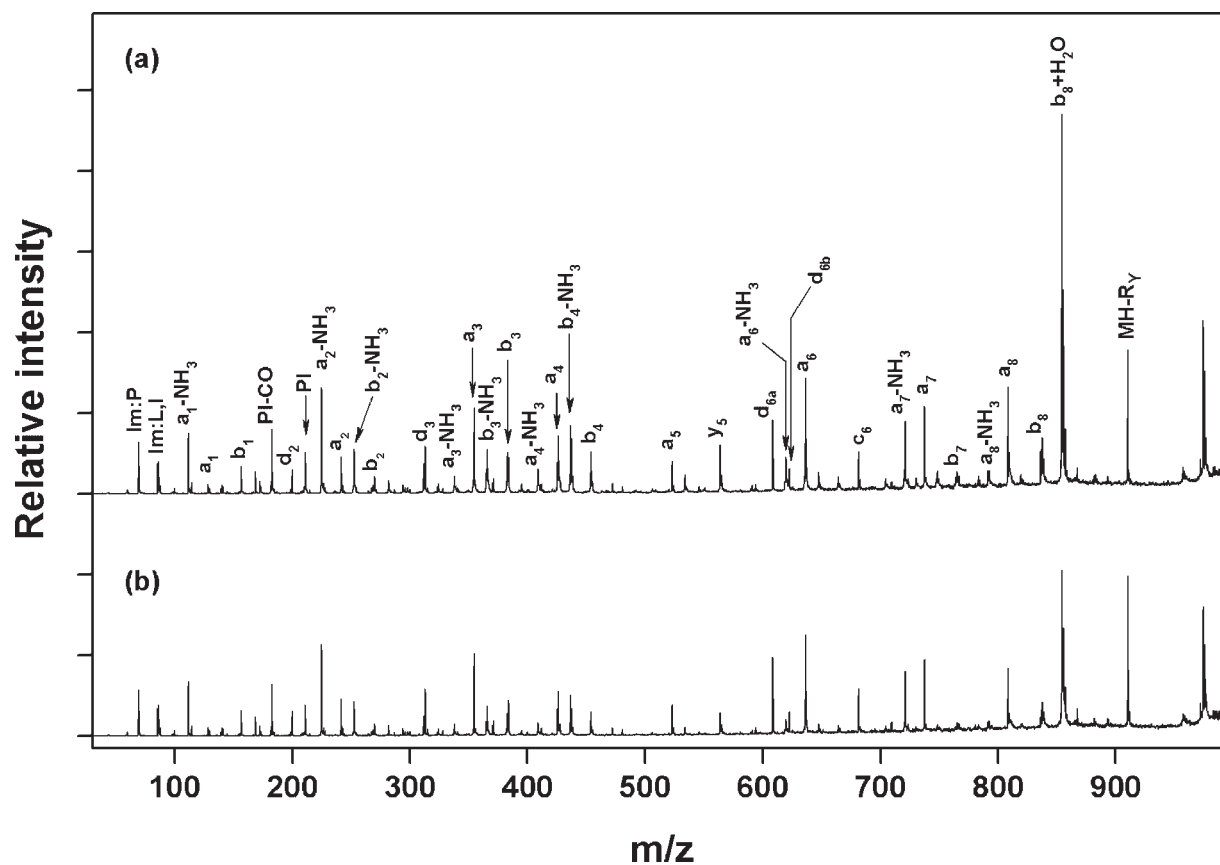


Figure 3. The laser-on spectra at 193 nm for the protonated RLLAPITAY recorded with the deflectors (a) off and (b) on, normalized to the photodepletion of the precursor ion.

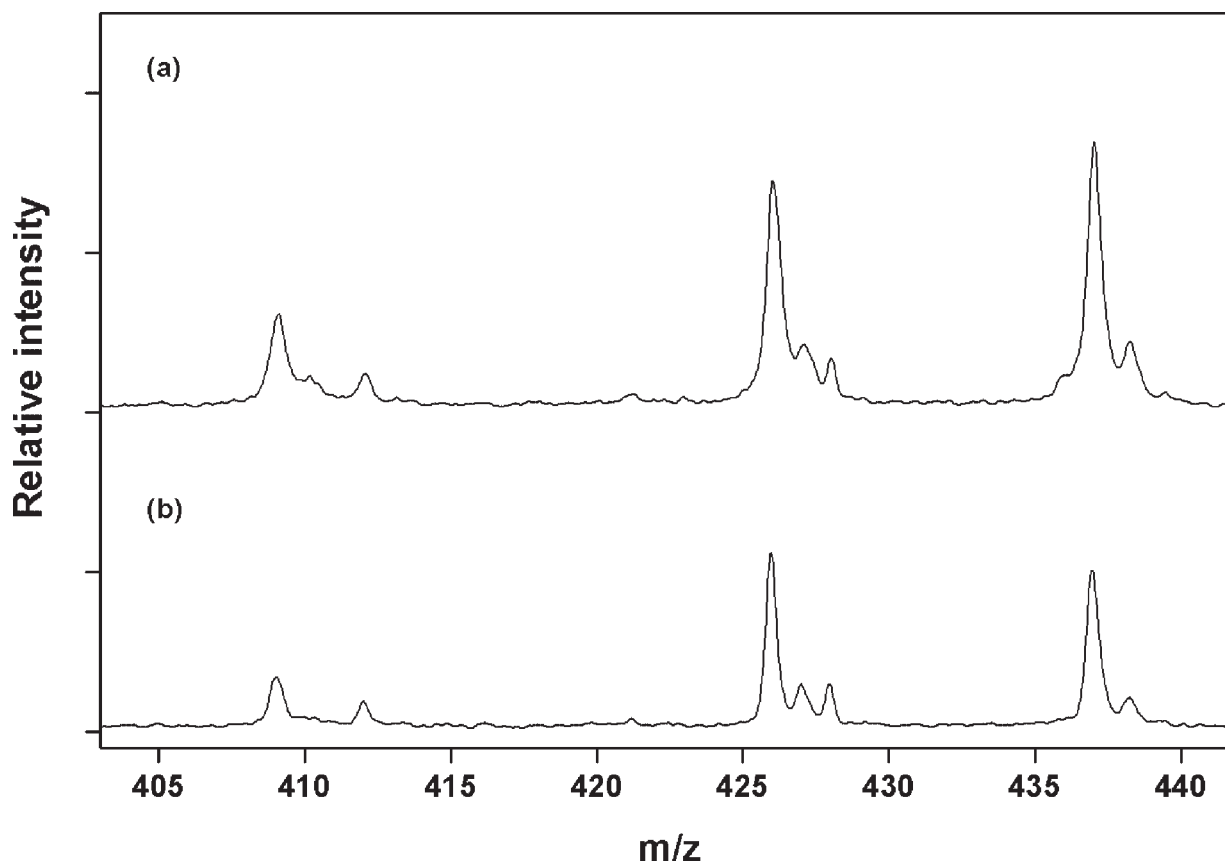


Figure 4. The m/z 405–440 region of the laser-on spectra in Fig. 3, with the deflectors (a) off and (b) on.

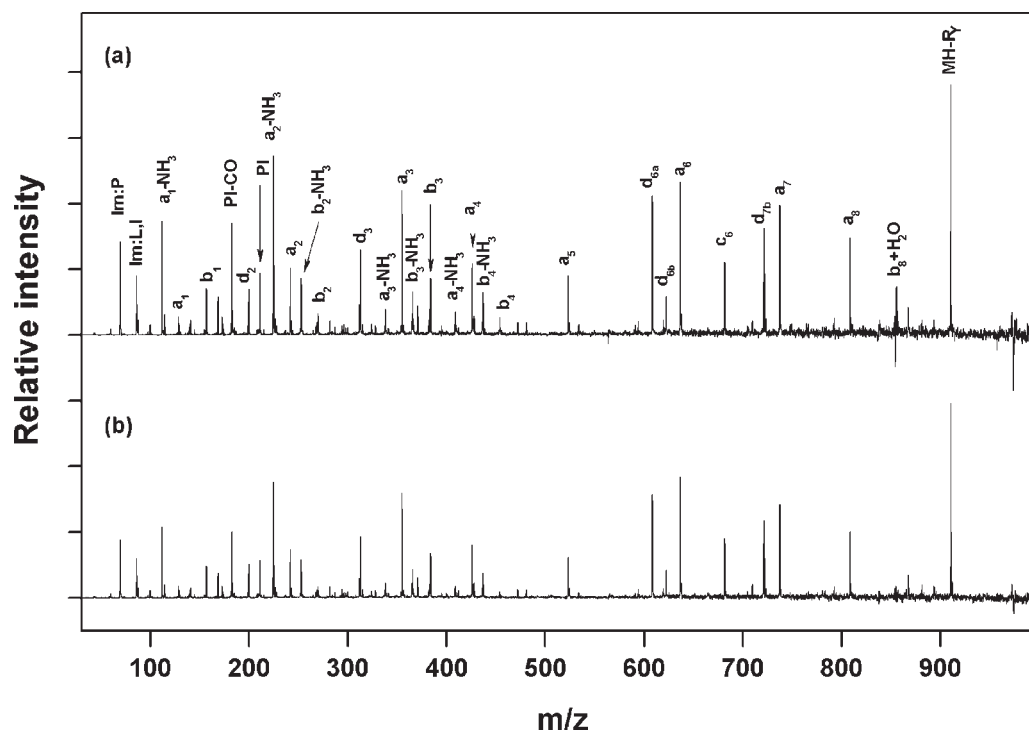


Figure 5. The 193 nm PD spectra of the protonated RLLAPITAY with the deflectors (a) off and (b) on obtained by subtracting the laser-off (Fig. 2) spectra from the corresponding laser-on (Fig. 3) spectra.

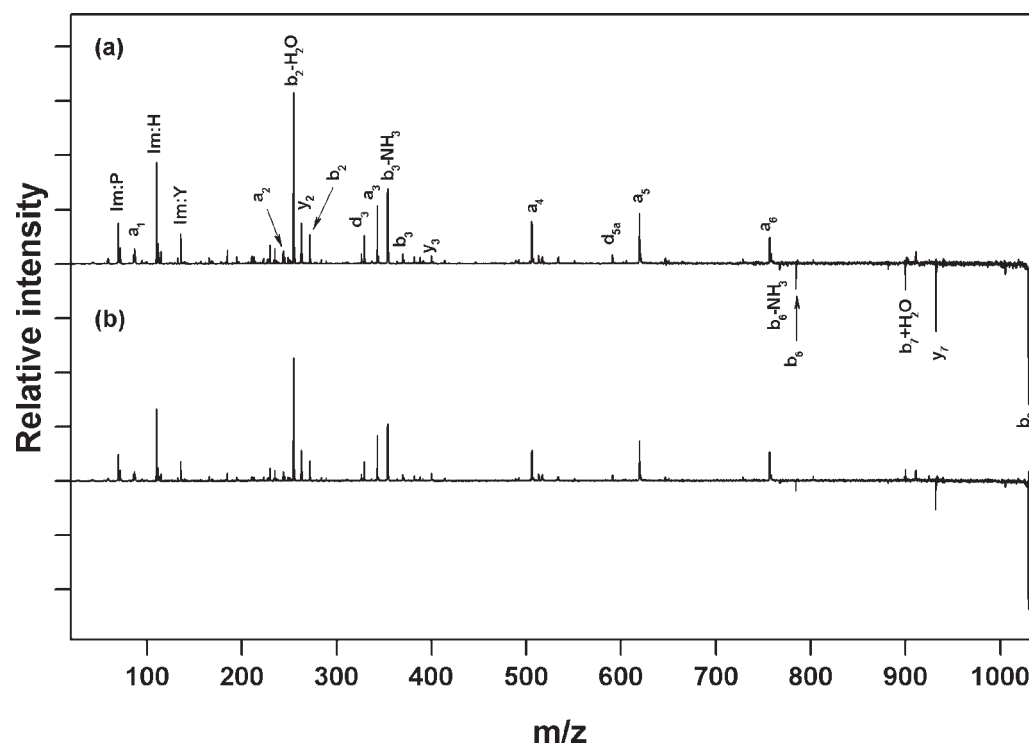


Figure 6. The 266 nm PD spectra of the protonated angiotensin II ($[\text{DRVYIHPF}+\text{H}]^+$, m/z 1046.5) recorded with the deflectors (a) off and (b) on.

the PSD product ion intensity at the first time-focus by the deflectors reduces the amount of photodepletion of the PSD product ion and results in the positive signal at this m/z . It is to be mentioned that there can be another origin to a negative intensity in a PD spectrum.

Suppose that a reaction is very favorable when the precursor ion has barely enough internal energy for dissociation and its product appears prominently in the PSD (laser-off) spectrum. When the internal energy increases by photoabsorption, this channel may lose its competitive edge to others and its product may appear less prominently in the laser-on spectrum. Then, even when the PSD product ion does not undergo PD, the intensity of the corresponding peak in the PD spectrum (laser-on minus laser-off) can appear negative. This may be responsible for the fact that some negative signals in Fig. 5 are not reduced by the deflection systems as much as theoretically expected.

There are other differences between the deflector-off and -on spectra observed for minor peaks. Careful inspection of Fig. 5 and Fig. 6 also, reveals that peaks in the two spectra do not necessarily correlate. There are more minor peaks in the deflector-off spectra than in the deflector-on spectra. The background levels in the deflector-off spectra are higher than in the deflector-on spectra also. All these affect the PD spectra obtained via spectral reduction, as shown in Fig. 7 derived from the spectra in Fig. 5. Overall, there are more minor peaks in the deflector-off spectrum, most of which must be spurious such as the strong feature at around m/z 855. In some cases, the situation is the other way around, such as the appearance of y_5 (565.1) in the deflector-on spectrum which is absent in the deflector-off spectrum.

Finally, it should be mentioned that the background level at high- m/z range in each PD spectrum, Figs. 5 and 6, is

slightly lower than that at low- m/z range, or is negative, both in the deflector-off and -on cases. Namely, chemical noise is less in the laser-on spectrum than in the laser-off one. This arises because the precursor ions with small internal energy, which would have dissociated inside the reflectron, dissociate rapidly upon photoabsorption and hence contribute less to the chemical noise level.

Resolving power

When a reflectron with a linear potential (constant field)^{25–27} inside is used in the second stage of TOF-TOF, the resolution for a fragment ion deteriorates rapidly as its m/z decreases. For such instruments, it is usual to record tandem mass spectra at several reflectron voltages and stitch the results together.¹⁸ The present instrument, designed with an additional quadratic potential component in the reflectron, shows much better resolution for fragment ions.¹⁹ Kinetic energy release in dissociation also deteriorates fragment ion resolution, especially in the low- m/z range. It has been shown earlier that the fragment ion resolution in a PSD spectrum improves with the use of the deflection system which eliminates fragment ions generated in the front part of the field-free region. Taking the PI-CO (m/z 182.8) ion shown as insets in Fig. 2 as an example, its full width at the half maximum (FWHM) in the deflector-off and -on spectra are 0.84 and 0.42 amu, respectively, corresponding to 220 and 440 in resolving power. FWHMs of the same peaks in the laser-on spectra are 0.35 amu with the deflectors off and on, corresponding to 520 in resolving power. With the PSD contributions subtracted, FWHMs in the deflector-off and -on PD spectra become 0.32 amu, equivalent to 570 in resolving power. Another example is the PI (m/z 210.9) ion. The resolving powers at this peak in the deflector-off PSD,

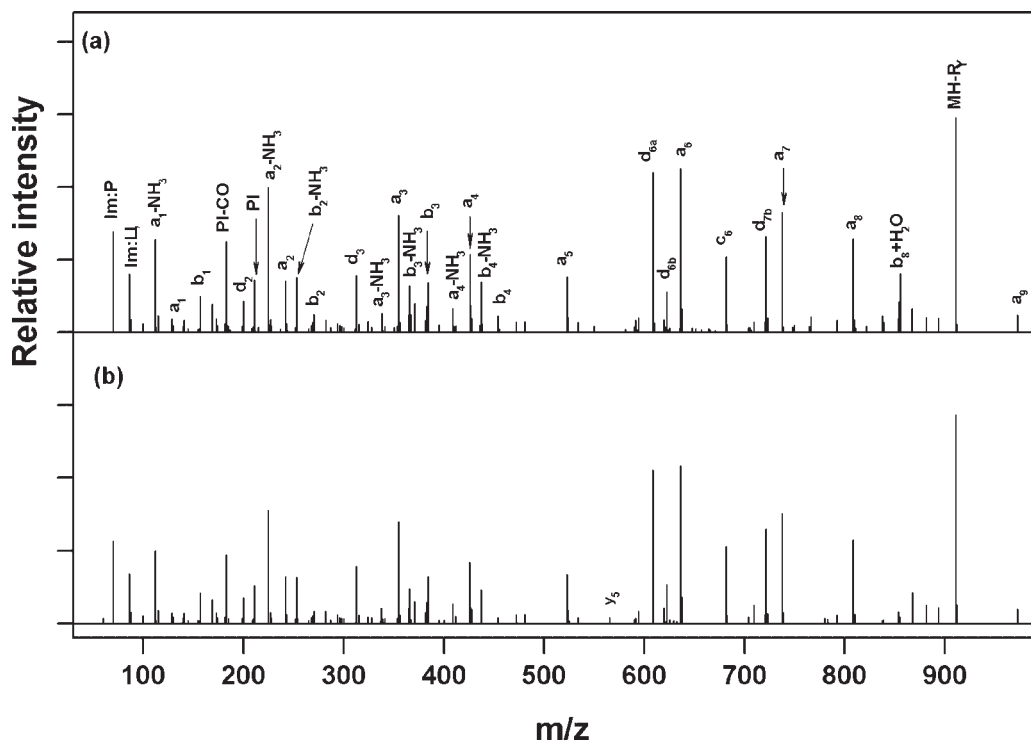


Figure 7. The 193 nm PD spectra of the protonated RLLAPITAY after spectral reduction. Deflectors (a) off and (b) on.

laser-on, and PD spectra are 260, 530, and 640, respectively, while those in the deflector-on spectra are 500, 590, and 640. The situation has been found to be similar for other peaks in the low- m/z region. It is to be emphasized that unit mass resolution has been achieved when the deflection system was used even at m/z as low as 50 for the laser-on and PD spectra without switching the reflectron voltage.

Finally, it should be mentioned that a PD peak has been found to be invariably narrower than the corresponding peak in the PSD spectrum even when the deflectors are turned on. This is an interesting result in itself considering that the kinetic energy release in PD is not likely to be smaller than that in PSD. A plausible explanation may be that PD occurs within a short distance from the first time-focus and hence its products are rather well time-focused while PSD occurs over the entire length between the deflector end and the reflectron entrance. This hypothesis, if found to be correct, has important implications in the kinetics and dynamics of the PD process and in optimization of the PD-tandem-TOF instrumentation. A detailed investigation is being planned.

SUMMARY AND CONCLUSIONS

Since a PSD product ion moves with nearly the same velocity as its precursor, it is not possible to eliminate such an ion in tandem-TOF mass spectrometers with conventional design. This can cause a problem in PD-tandem-TOFMS, and in CAD tandem-TOFMS also, because not only the intended precursor ion but also its PSD products can undergo activation and dissociation. It has been demonstrated in this work that a deflection system consisting of four deflectors located between the ion source exit and the first time-focus of the instrument can eliminate most of the PSD product ions formed before the PD laser irradiation spot. It has been found that the deflection system does not affect the performance of the instrument like a MALDI-TOF spectrometer. Instead, using this system has been found to improve the resolving power in the PSD spectra noticeably.

Since the intensities of PSD product ions are much weaker than that of the precursor ion for ordinary peptide samples such as those studied in this work, interference from PSD product ions in the PD spectra has not been significant. Namely, use of the deflection system has been helpful to determine the presence or absence of minor peaks only. However, the system would be useful in detailed mechanistic studies in which observation of a particular reaction path, even if not dominant, often provides a clue to the overall mechanistic pathways. The system would be especially useful when abundant PSD product ions are formed such as for phosphorylated peptides.²⁸

With the use of an ion gate, ion pulse-laser pulse synchronization, and the deflection system developed in this work, the present instrument provides an excellent

selection of a precursor ion, which will be useful to obtain PD spectra almost free from contamination. The deflection system is now being used on a routine basis in this laboratory.

Acknowledgements

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