Cyclization and Rearrangement Reactions of Fragment Ions of Protonated Peptides: IRMPD and Theoretical Studies

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Peptide sequencing in proteomics is mainly achieved by tandem mass spectrometry (MS/MS) of protonated peptides. In these experiments peptide ions are excited by collisions with inert gases (collision-induced dissociation (CID)) to induce fragmentation and the resulting product ion spectra are used to decipher the sequences. The product ion spectra of protonated peptides are usually dominated by sequence informative *b*, *a*, and *y* fragments, which are formed in a complex reaction cascade [1]. To facilitate rapid processing of the large number of spectra routinely produced in high-throughput proteomics experiments, various bioinformatics tools have been developed. These programs utilize fragmentation models to generate theoretical spectra for candidate sequences and various mathematical measures to assess similarity between these theoretical spectra and the experimental MS/MS spectra. One of the basic assumptions inherent to the current implementation of this strategy is that peptide ions or their fragments dissociate on *direct* fragmentation pathways, which do not introduce rearrangements of the original sequences.

Recent studies [2-4] indicate that the dissociation chemistry of *a and b* ions cannot be universally described by considering only *direct* fragmentation chemistries. For example, linear *b* structures can undergo head-to-tail cyclization to form a macrocyclic isomer which can open up at any amide bond to regenerate linear isomers. This chemistry in all but the case where the original sequence is regenerated leads to linear *b* isomers with scrambled sequences. IRMPD and theoretical studies on this 'scrambling' chemistry of *b* ions and rearrangement pathways of *a* fragments will be reviewed in this presentation.

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