Peptides chasing their tails – what infrared spectroscopy can tell us about peptide dissociation chemistry

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Peptides are dissociated in mass spectrometers to derive their amino acid sequence. In collision-induced dissociation (CID), abundant amide backbone cleavage is observed, resulting in N-terminal **b** and C-terminal **y** fragments. While **y** fragments adopt a normal peptide structure, **b** fragments exhibit a C-terminal amide C=O that must be stabilized by a nucleophilic attack. It was generally assumed that another carbonyl oxygen engages in this attack, resulting in a five-membered ring oxazolone structure. This has been confirmed by infrared photodissociation spectroscopy [1]. However, peptides exhibit other nucleophiles, such as side-chain groups, and the N-terminal amino group. When the latter group takes part in a "head-to-tail" nucleophilic attack, this gives rise to a macrocycle structure, where the N- and C-terminal parts of the molecule are fused together. Re-opening of this structure at a different amide bond results in sequence permutation [2], thus potentially leading to misidentification of the sequence. Once again, vibrational spectroscopy can yield insights for the presence of such macrocycle structures, based on diagnostic vibrations [3]. Recent results on the competition between oxazolone and macrocycle formation will be presented for a number of peptide systems. The trends so far suggest that the propensity to form the macrocycle structure increases with chain length of the fragment [4]. Moreover, some residues are shown to play an important role in dis/favoring macrocycle formation. It is expected that these studies will shed light on the processes that promote sequence permutation in CID, thus establishing how prevalent this phenomenon is.

[1] Polfer *et al., J. Am. Chem. Soc.* **2005**, 127, 17154.

[2] Harrison *et al., J. Am. Chem. Soc*. **2006**, 128, 10364.

[3] Polfer *et al., J. Am. Chem. Soc*. **2007**, 129, 5887.

[4] Chen *et al., J. Am. Chem. Soc*. **2009**, 131, 18272.