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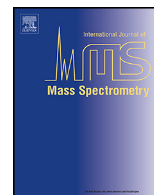

Intrinsic size parameters for palmitoylated and carboxyamidomethylated peptides

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ABSTRACT

Cross sections for 61 palmitoylated peptides and 73 cysteine-unmodified peptides are determined and used together with a previously obtained tryptic peptide library to derive a set of intrinsic size parameters (ISPs) for the palmitoyl (Pal) group (1.26 ± 0.04), carboxyamidomethyl (Am) group (0.92 ± 0.04), and the 20 amino acid residues to assess the influence of Pal- and Am-modification on cysteine and other amino acid residues. These values highlight the influence of the intrinsic hydrophobic and hydrophilic nature of these modifications on the overall cross sections. As a part of this analysis, we find that ISPs derived from a database of a modifier on one amino acid residue (Cys^{Pal}) can be applied on the same modification group on different amino acid residues (Ser^{Pal} and Tyr^{Pal}). Using these ISP values, we are able to calculate peptide cross sections to within ±2% of experimental values for 83% of Pal-modified peptide ions and 63% of Am-modified peptide ions. We propose that modification groups should be treated as individual contribution factors, instead of treating the combination of the particular group and the amino acid residue they are on as a whole when considering their effects on the peptide ion mobility features.

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Introduction

Advances in peptide identification by mass spectrometry (MS) and tandem MS-MS methods have dramatically improved the analysis of complex mixtures of proteins [1,2]. However, various co- and post-translational modifications that occur naturally, as well as modifications that occur as a part of sample work-up [e.g. the alkylation of cysteine (Cys) [3] and isotopic labeling of peptides for quantitative proteomics [4–6]], may complicate these analyses. Many alternations may occur in low concentrations; in addition, chemical modifications may decrease ionization efficiency, and introduce complexities in assignments of sequences [7,8].

Recently, ion mobility spectrometry (IMS) measurements of peptide ions have been introduced as a means to complement MS-MS-based peptide ion assignments [9–14]. The IMS approach introduces mass-independent constraints based on the peptide cross-section (Ω). From large numbers of cross section measurements it is possible to assess average contributions of each amino acid to the overall size by the derivation of intrinsic size parameters (ISP) for individual amino acids [9–14]. Amino acid size parameters have now been derived for a range of polypeptide chain lengths, charge states, as well as for polypeptide chains that are ionized with a range of different cations -e.g., hydrogen [9–12], alkali metal [13], alkaline-earth metal [14], and transition metal [15]. Once these values are determined, it is possible to use the ISP values to calculate cross sections for peptide sequences that have not been observed previously; such an approach provides a mass-independent parameter that can be used to test the veracity of assignments based on MS and MS-MS data, thus improving the reliability of such analyses [12,16].

In this paper, we present a first step in extending the use of ISPs to include peptide modifications. The effect of modification groups on peptide structures in the gas phase has attracted some interest [17–23]. For example, phosphorylation typically causes peptides to adopt structures that are more compact than non-phosphorylated peptide structures, even when differences in molecular weight are considered [17,18]. To date, IMS measurements have also been applied as a means of assessing locations of chemical cross-linking [19], phosphorylation [20,21], glycosylation [22], and methylation [23]. The work presented below focuses on two types of

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proteomics modifications found primarily on cysteine residues: carboxyamidomethylation [3,24,25] (designated as Cys^{Am} or C^{Am}), and palmitoylation (designated as Cys^{Pal} or C^{Pal}). Palmitoylation can also occur on hydroxyl- and amino-groups such as those found on serine, threonine, tyrosine, lysine, and the amino terminus, especially when glycine is the first residue [26]. Example structures of the Cys^{Am} residue and several palmitoylated residues (Cys^{Pal}, Thr^{Pal} and Gly^{Pal}) are shown in Fig. 1.

The Cys^{Am} modification is among the most common that is observed in proteomics studies. This modification is often introduced during sample workup upon addition of excess iodoacetamide (IAM). The irreversible alkylation reaction provides a modification that acts as a protecting group, preventing the reformation of disulfide bonds [3,24,25]. Below, we derive an ISP value for the Am modification to be 0.92 ± 0.04, which is smaller than the average intrinsic size (1.00, by definition) that is based on the

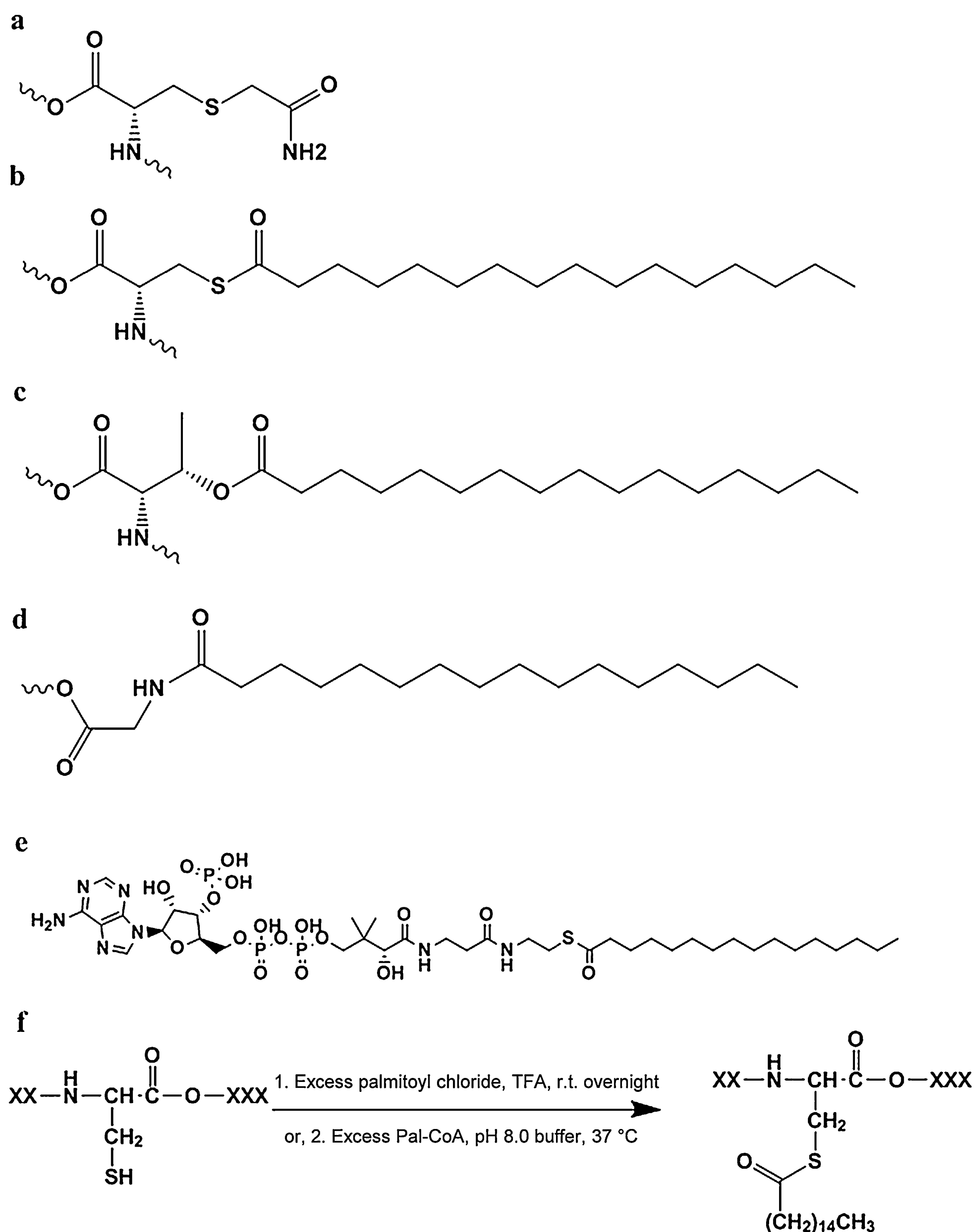

Fig. 1. Sample molecular structures and reaction schematics for the carboxyamidomethylation (Am) or palmitoylation (Pal) modifications. (a) Carboxyamidomethylated cysteine residue (Cys^{Am}). (b) Palmitoylated cysteine residue (Cys^{Pal}), with the modification on the thiol group. (c) Palmitoylated threonine residue (Thr^{Pal}), with the modification on the hydroxyl group. (d) N-palmitoylated glycine residue (Gly^{Pal}), with the modification on the N-terminus of a peptide or protein. (e) Palmitoyl coenzyme A (Pal-CoA). (f) Palmitoylation reaction schematics. (f-1) Reaction via palmitoyl chloride in TFA solution. (f-2) Reaction via Pal-CoA in pH 8.0 phosphate buffer.

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