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Mass spectrometry signal enhancement by reductive amination

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ABSTRACT

Organosulfur compounds (OSCs) subjected to reductive amination in the presence of formaldehyde exhibited increased mass spectrometry signal intensities. In this study, four OSCs including *S*-allyl cysteine, *S*-allylcysteinine sulfoxide, *S*-methylcysteine and *S*-ethylcysteine were generated using isotopic formaldehyde, and mass spectrometry signal intensities of modified and unmodified OSCs were compared. This comparison involved tandem mass spectrometry infusion and detection techniques, such as selected ion monitoring (SIM) and multiple reaction monitoring (MRM). The signal intensities of modified OSCs increased from 2.6 to 39.2 fold by infusion, from 50.0 to 479.6 fold by SIM, and from 146.4 to 2494.8 fold by MRM. Compounds bearing primary amine groups reacted with formaldehyde in high yield and underwent reductive amination in the presence of sodium cyanoborohydride to form a dimethyl group on these amine groups. The modified OSCs showed enhanced intensities because the electron donating dimethyl groups increase their basicity. This signal enhancement is expected to improve the limit of detection in absolute quantification and structural characterization. Therefore, reductive amination involving primary amine groups may find application in the enhancement of mass spectrometry signal intensities.

1. Introduction

Comparative proteomics typically relies on stable isotope labeling and tandem mass spectrometry (MS) coupled with the shotgun approach or two-dimensional gel electrophoresis to achieve global protein identification and profiling [1–3]. Amine containing metabolite profile including 20 amino acids and 15 amines has been generated by stable isotope labeling through the reductive amination of primary amine groups in the presence of formaldehyde [4]. Glycosylation variants have been relatively quantified using isotopic formaldehyde [5].

Reductive amination, described as stable isotope dimethyl labeling, has also been utilized to enhance the signal intensity of saccharides by matrix-assisted laser desorption ionization MS [6]. Reductively aminated oligosaccharides have been detected by high-performance liquid chromatography (HPLC)/electrospray ionization (ESI) MS [7,8] and capillary electrophoresis (CE) [9], and have shown MS signal enhancement. However, organic synthetic conditions are sometimes unsuitable for protein and peptide analysis.

In the early period, however, mobile phase composition adjustment methods were popular for proton transfer efficiency evaluation. Proton scavengers, such as ammonium, methylamine, trimethylamine, diethylamine and triethylamine [10–12], were compared because proteins exhibiting a high charge state during mass spectrometry fragmentation by collision-induced dissociation were more sensitive than those presenting a lower charge state [13]. However, the detection of post-translational modifications, such as protein phosphorylation and glycosylation, and the identification of signal charge states require protein or peptide modification associated with ion charge enhancement. Such a charge enhancement has been observed by electron transfer dissociation (ETD) tandem MS [14,15]. Furthermore, the orifice diameter of the spray tip was altered

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