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Intermolecular Phosphoryl Transfer Between Serine and Histidine Residues

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Abstract: A novel intermolecular phosphoryl transfer from *O*-trimethylsilyl-N-(*O*, *O*-diisopropyl) phosphoryl serine trimethylsilyl ester to N, N'–bis(trimethylsilyl) histidine trimethylsilyl ester was studied through electrospray ionization mass spectrometry (ESI-MS). It was proposed that the transfer reaction went through penta-coordinated phosphorus intermediate.

Keywords: Intermolecular phosphoryl transfer, penta-coordinated phosphorus, ESI-MS.

Phosphoryl transfer is a typical biochemical reaction[1]. Many enzymes' activity is regulated through the phosphorylation and dephosphorylation mechanism[2], which can be performed either intra- or inter-molecularly. In proteins, phosphorylation and dephosphorylation sites often contain serine, threonine, aspartic acid or histidine residues. For example, signal transduction occurs through transfer of the phosphoryl group from the histidine residue of histidine protein kinase (HPK) to the aspartic acid residue in the response regulator (RR), and eventually to inorganic phosphate[3]. So it is very important to study phosphoryl transfer reaction of life process. However, because proteins have complex structures and large molecular weight, it is better to mimic proteins' phosphoryl transfer through small amino acid residues.

This paper described a novel intermolecular phosphoryl transfer from *O*-trimethylsilyl-N-(*O*,*O*-diisopropyl) phosphoryl serine trimethylsilyl ester **1** to N, N'–bis(trimethylsilyl) histidine trimethylsilyl ester **2**. Equimolar amount of **1** and **2** was mixed and reacted at 30 °C (room temperature). After three days, the reaction products were acidified with 5 mol/L HCl, and crude products in water phase were detected by ESI-MS. It was found that histidine had self-assembled into di-, tri-, tetra-peptides (**Figure 1**), peaks at *m/z* 293, 430, 567 corresponding to His-His, His-His-His, His-His-His-His, respectively. Structures of these peptides were further confirmed by ESI-MS(n) (**Table 1**).

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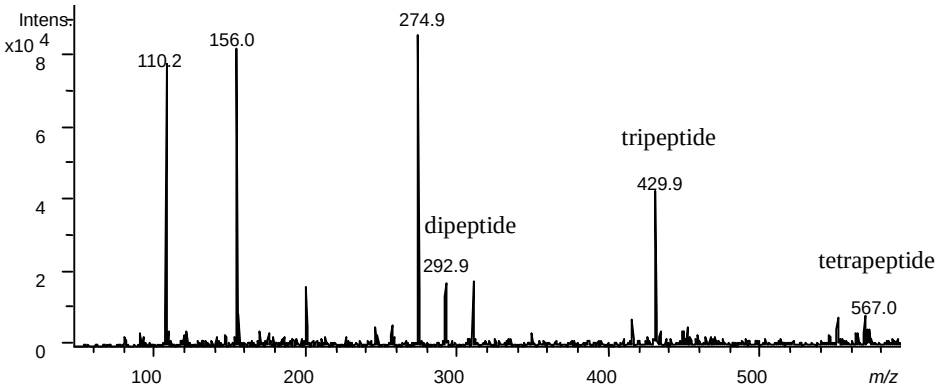
Figure 1 Positive ion ESI-MS spectrum of histidine oligopeptides



The above results suggested that the amino group of N,N'–bis(trimethylsilyl) histidine trimethylsilyl ester **2** attacked the phosphoryl group of *O*-trimethylsilyl-N-(*O*, *O*-diisopropyl) phosphoryl serine trimethylsilyl ester **1**, then intermolecular phosphoryl transfer produced N-trimethylsilyl-N-(*O*, *O*-diisopropyl) phosphoryl histidine trimethylsilyl ester **4**. It was proposed that the transfer reaction went through penta-coordinated phosphorus intermediate **3** (**Scheme 1**). Then histidine residue of **4** was activated through forming carboxylic-phosphoric mixed anhydride **5**, which could be considered as the model of aminoacyl-tRNA. And it could be coupled with **2** to produce the His-His, His-His-His, His-His-His-His, oligopeptides sequentially[4,5].

This paper described an intermolecular phosphoryl transfer without participation of the kinase, it provided a new method to use small amino acids residues to mimic and study proteins' phosphoryl transfer mechanism.

Scheme 1

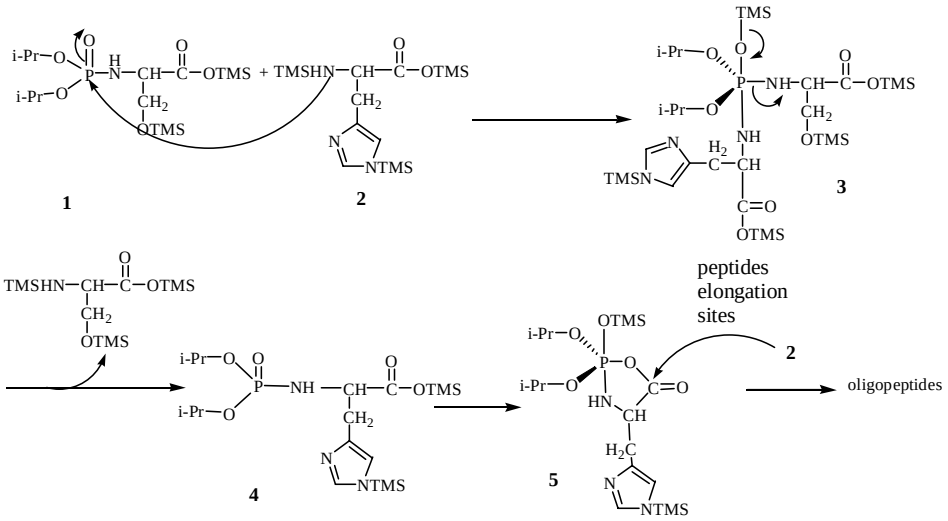


Table 1 Positive ion ESI-MS(n) datas for reaction products

Compounds	Precursor ions $[M+H]^+$	Fragment ions (relative intensity %)
His-His	293	293(28), 275(100)
	275	258(100),214(19),202(55),110(25)
His-His-His	430	394(63), 293(28), 275(100)
His-His-His-His	567	549(40), 394(63), 293(28), 275(100)

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