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PREBIOTIC CHEMISTRY

# Selective Formation of Ser-His Dipeptide via Phosphorus Activation

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**Abstract** The Ser-His dipeptide is the shortest active peptide. This dipeptide not only hydrolyzes proteins and DNA but also catalyzes the formation of peptides and phosphodiester bonds. As a potential candidate for the prototype of modern hydrolase, Ser-His has attracted increasing attention. To explore if Ser-His could be obtained efficiently in the prebiotic condition, we investigated the reactions of *N*-DIPP-Ser with His or other amino acids in an aqueous system. We observed that *N*-DIPP-Ser incubated with His can form Ser-His more efficiently than with other amino acids. A synergistic effect involving the two side chains of Ser and His is presumed to be the critical factor for the selectivity of this specific peptide formation.

**Keywords** Ser-His · Hydrolase prototype · Synergistic effect · Selective formation of peptide bonds

**Highlights**
1. *N*-DIPP-Ser treated with His can form *N*-phosphoryl Ser-His specifically with high efficiency, while Ala, Asp, Pro, and Ser cannot.
2. The possible mechanism is illustrated as the synergistic effect of the two side chains of Ser and His.
3. This study provides clear evidence for the effective acquisition of Ser-His in prebiotic conditions.

Wanyun Shu and Yongfei Yu contributed equally to this work.

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## Introduction

According to a previous report, biological functional molecules, such as RNA, proteins and lipid precursors, can all be produced in diverse ways from several small molecules exposed to UV light with certain inorganic salts as catalysts. (Patel et al. 2015). The emergence of a hydrolase precursor in the process of prebiotic chemical evolution would be a milestone. Based on the previous work in our lab, *N*-phosphoryl amino acids possess manifold biochemical reaction activities that could produce the above-mentioned building blocks for life, therefore they could be regarded as mini-activating enzymes (Ni et al. 2015).

During the investigation on the reaction of *N*-diisopropyl phosphoryl serine (*N*-DIPP-Ser) with His, seryl histidine dipeptide (Ser-His) was discovered. This dipeptide has attracted considerable attention because of this molecule's diverse biological functions. Ser-His not only promotes the condensation of amino acids (Gorlero et al. 2009) and ribonucleotides (Wieczorek et al. 2013) but also cleaves DNA and proteins reversibly (Ma et al. 2007; Li et al. 2000). Additionally, Ser-His can indirectly promote the growth of membranes (Adamala and Szostak 2013). Therefore, Ser-His is a distinctive dipeptide that seems to be a candidate for the evolutionary prototype of modern hydrolase. In terms of its synthesis, however, Ser-His is still not easy to be obtained, since it usually needs coupling agents and group protections. To date, it has been rarely reported if and how Ser-His occurs in the prebiotic condition.

Based on its activities in self-assembly peptide formation, *N*-DIPP-Ser was used in this study as a model to investigate peptide formation with other amino acids in aqueous solution. We observed that *N*-DIPP-Ser incubated with His can form Ser-His more efficiently than with other tested amino acids, such as Ala, Pro, Asp and Ser. The five amino acids represented: two hydrophobic amino acids with branched or cyclic side chains and three hydrophilic ones with acid, alkali, or neutral side chains. These tested amino acids are representative of ancient amino acids except His (Trifonov 2000). However, the synthesis of histidine in simulated prebiotic conditions has also been reported (Shen et al. 1990). To a certain extent, these results indicate that Ser and His are the best partners among the ancient amino acids because they have a greater tendency to form dipeptides together with the activation of phosphorus. This finding illustrates that Ser-His could be obtained spontaneously and competitively in the prebiotic condition. Therefore, it is reasonable to believe that Ser-His might be the potential candidate for the evolutionary prototype of modern hydrolase.

## Materials and Methods

### Materials and Instruments

#### *Materials*

Organic reagents, such as diisopropylphosphite (DIPPH), triethylamine ($Et_3N$), carbon tetrachloride ($CCl_4$) and ethanol, were acquired from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China).

Serine, alanine, aspartic acid, histidine, proline, imidazole and standard Ser-His dipeptides were ordered from GL Biochem Ltd. (Shanghai, China). Sodium chloride and sodium hydroxide were purchased from Sigma-Aldrich (Saint Louis, MO, USA). Unless otherwise

specified, all chemicals and solvents were analytical reagents used without further purification. ODS $C_{18}$ packing was purchased from Daisogel (Osaka Soda, Osaka, Japan).

HPLC-grade methanol and acetonitrile were purchased from Merck Co. (Darmstadt, Germany). Water was purified by a Milli-Q purification system (Millipore, Bedford, MA, USA).

*Instruments*

## High-Performance Liquid Chromatography

The HPLC system was composed of an Agilent 1260 analytical HPLC system (Agilent Technologies, USA) equipped with a G1315D Diode Array Detector (DAD); DataAnalysis 4.1 software (Bruker Daltonics, Germany) was used for data processing.

A reversed phase PGC column (2.1 × 150 mm, 3 μm, Thermo Fisher Scientific, USA) was used for the analysis and separation of dipeptide products. The column was maintained at room temperature. Chromatography experiments were carried out in a gradient mode with acetonitrile and water. Both water and acetonitrile of HPLC grade were freshly filtered with a 0.22 μm filter membrane and degassed by an ultrasonic device for 30 min. The percentage of acetonitrile was changed linearly as follows: 0 min, 95%; 7 min, 95%; 24 min, 70%; 35 min, 70%; 40 min, 30%.

The flow rate was 0.2 mL·min$^{-1}$ and the detection wavelength was set at 210 nm.

## Mass Spectrometry

HPLC-ESI-MS$^n$ analysis was performed on the Agilent HPLC 1260 system described above coupled with a MicroTOF Q II mass spectrometer (Bruker Daltonics, Germany) equipped with an ESI source. The samples were infused directly into the mass spectrometer in positive mode from the eluent of HPLC system because of the low flow rate of 0.2 mL·min$^{-1}$. The instruments used helium as the collision gas, and the experimental parameters were set as follows: nebulizer gas, 2.0 psi; spray voltage, 4.5 kV; dry gas, 8.0 L·min$^{-1}$, and drying temperature, 200 °C. CID-MS/MS analysis was performed at collision energies of 22 to 34 eV.

## ODS $C_{18}$ Column Chromatography

*N*-DIPP-Ser-His was isolated and purified by ODS $C_{18}$ column chromatography and eluted with water (95%, v/v) and acetonitrile (5%, v/v).

## Methods

*Synthesis of Diisopropyl Phosphoryl Serine (N-DIPP-Ser)*

*N*-DIPP-Ser can be synthesized according to published work (Ji et al. 1988). The product was confirmed by NMR and MS. Related spectra are provided as supporting information (**Figs. S1-S4**). *N*-DIPP-Ser is an unstable compound that must be kept at −20 °C and used within a week.

*General Method to Form Dipeptides Containing Ser*

An amino acid (1 M, namely, Ser, Ala, Asp, Pro or His) was added into the 1 M *N*-DIPP-Ser aqueous solution and incubated at 37 °C for different times. Two control groups of Ala with *N*-DIPP-Ser were performed by adding imidazole (1.0 equivalent of Ala) and Ser-His (cat.) respectively.

*Competitive Experiments of Five Amino Acids with N-DIPP-Ser*

Five amino acids, namely Ser, Ala, Asp, Pro and His, at concentrations of 0.2 M each, were mixed with 1 M *N*-DIPP-Ser and proper amounts of imidazole to maintain pH at 6 and kept at 37 °C for 24 h.

Besides, the pH values of another competitive experiment groups without imidazole were adjusted to 3, 7, or 10 with NaOH (20 M).

*Analysis and Identification of Dipeptides Containing Ser*

The reaction mixtures were diluted to 1 mM solution with distilled water, treated with a 0.22 μm needle filter and subsequently analyzed by HPLC-ESI-$MS^n$.

*Isolation of N-DIPP-Ser-His*

*N*-DIPP-Ser-His, as the precursor of Ser-His in the reaction system of *N*-DIPP-Ser with His, was further isolated and purified with an ODS $C_{18}$ column. The structure of *N*-DIPP-Ser-His was characterized by MS and NMR (**Figs. S5-S7**). The related spectra data were as follows: ESI-MS in positive mode, *m/z* 407, $^{31}$P CPD NMR (202 MHz, $D_2O$) δ 6.90 (s). $^{31}$P NMR (243 MHz, $D_2O$) δ 6.90 (dd, $J$ = 16.2, 7.7 Hz). $^{1}$H NMR (400 MHz, $D_2O$) δ 8.50 (dd, $J$ = 10.9, 1.2 Hz, 1H), 7.20 (s, 1H), 4.57 ~4.46 (m, 2H), 4.39 (dt, $J$ = 12.0, 6.1 Hz, 1H), 3.79~3.62 (m, 3H), 3.24~2.99 (m, 2H), 1.19 (ddt, $J$ = 17.2, 13.5, 5.7 Hz, 12H), and $^{13}$C CPD NMR (126 MHz, $D_2O$) δ 175.66, 172.79, 172.75, 133.14, 129.34, 116.85, 73.47, 73.41, 73.36, 63.00, 62.95, 56.87, 54.18, 27.24, 22.89, 22.86, 22.79.

## Results and Discussion

It has been reported since 1969 that oligopeptides can be acquired in the presence of certain amino acids and inorganic phosphorus agents, such as linear or cyclic polyphosphate (Rabinowitz et al. 1969). Organic phosphorylation agents, such as diisopropyl phosphite (DIPPH), have been used to synthesize *N*-phosphoryl amino acids (Zhang et al. 2004; Ji et al. 1988), which have various biochemical activities, including peptide formation. These reactions all involve a penta-coordinate phosphorus intermediate formed from *N*-phospho-α-amino acids (Zhao et al. 1995). The related mechanism was determined by Fu, Hua; it involves the activation of an amino acid, the elongation of the peptide chain, and the termination of the elongation reaction (Fu et al. 1999). In 2002, Chen *et al.* observed that *N*-DIPP-Ser-His can be produced in aqueous solution when *N*-DIPP-Ser is treated with His at pH 8.0 (Chen et al. 2002). However, the yield was fairly low, measuring approximately 5%~6%(Quantification by $^{31}$P NMR).

## Difference in Dipeptide Formation among Five Amino Acids without pH Control

In this study, the five tested amino acids were respectively added to the aqueous solution of *N*-DIPP-Ser without any pH control. All reaction processes were traced through $^{31}$P CPD NMR (Fig. 1a). For all five reactions, except for three different hydrolysis products at −0.07 ppm, −0.67 ppm, and − 1.39 ppm identified in detail by $^{31}$P NMR (**Fig. S8**), a new unstable and unknown compound was observed at 6.16 ppm, which is on the right side of the raw material *N*-DIPP-Ser at 7.07 ppm in $^{31}$P CPD NMR spectra. This compound was preliminarily assigned as a reaction product with P-N bonds, such as *N*-phosphoryl dipeptide or *N*-monoisopropyl phosphoryl serine. Among these products, *N*-phosphoryl dipeptide has been affirmed in previous work as the precursor of the corresponding dipeptides (Chen et al. 2002). As displayed in Fig. 1a, *N*-DIPP-Ser incubated with His is more difficult to hydrolyze than other tested amino acids. Nevertheless, the hydrolysis products could also get more and more over time. The $^{31}$P NMR stack spectra of the reactions of 1 M *N*-DIPP-Ser with 1 M His in different reaction times is shown in Fig. 1b.

It is well-known that His can be used as a buffer and its side chain imidazole group has catalytic functions (Fitz et al. 2008). Because of the acidity of *N*-DIPP-Ser, the pH value of 1 M *N*-DIPP-Ser reaction solution with 1 M Ala is approximately 3. Hence, as a comparison, a tracking experiment of 1 M *N*- DIPP-Ser with 1 M Ala and 1 M imidazole (to keep the same pH as (b)) was also performed and monitored by $^{31}$P NMR. The results are shown in Fig. 1c. Comparing Fig. 1b with **1c**, *N*-DIPP-Ser is more active with His than Ala at the same pH condition. It is notable that the only difference between His and Ala is the extra side chain imidazole group of His. Figure 1c also indicates that the adscititious imidazole could not promote the formation of peptide products even under the same pH condition, but rather has a clear inhibiting effect. This finding means that the imidazolyl group combined with an α-amino group, typical case as His, can promote the formation of peptide bonds.

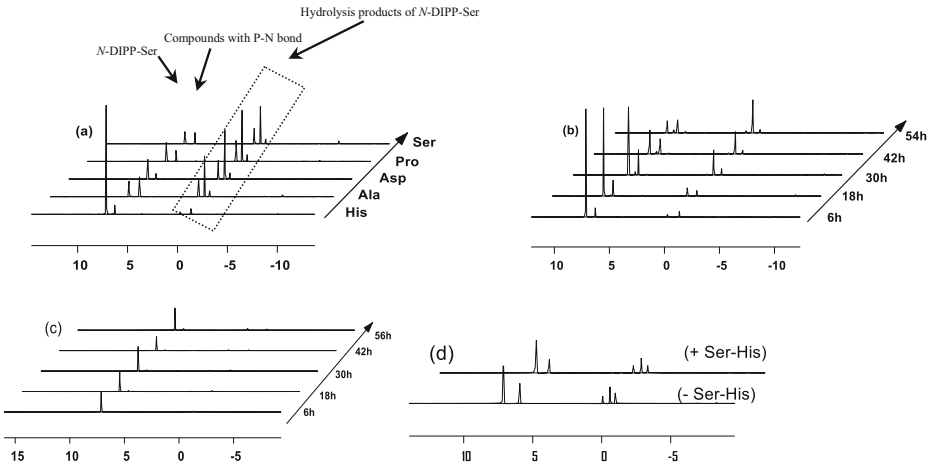



**Fig. 1** **a** Stack spectra of incubation reactions of 1 M *N*-DIPP-Ser with 1 M His, Ala, Asp, Pro, and Ser, respectively for 6 h. **b** The stack spectra of incubation reactions of 1 M *N*-DIPP-Ser with 1 M His (pH = 6) for 6 h, 18 h, 30 h, 42 h, 54 h. **c** The stack spectra of incubation reactions of 1 M *N*-DIPP-Ser with 1 M Ala and 1 M imidazole (kept pH as (**b**), approximately 6) for 6 h, 18 h, 30 h, 42 h, 54 h. **d** The spectra of incubation reactions of 1 M *N*-DIPP-Ser and 1 M Ala with (+) and without (−) Ser-His both for 6 h (cat.0.1 M)

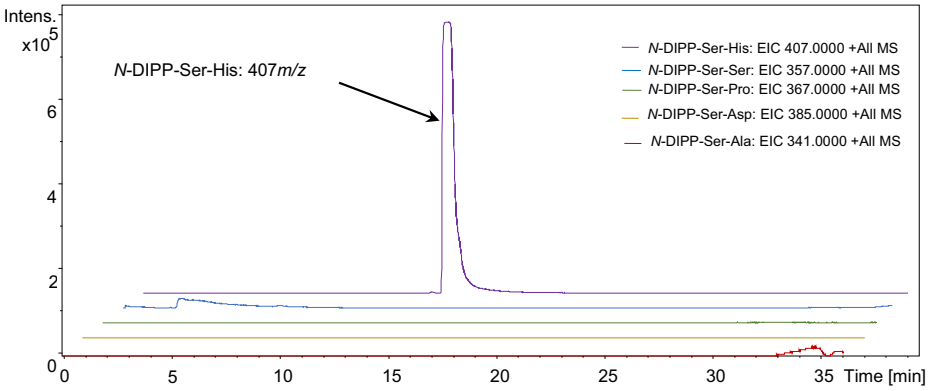



**Fig. 2** HPLC-ESI-MS analysis of the reactions of *N*-DIPP-Ser with five amino acids respectively. EIC is short for extracted ion chromatogram

Since Ser-His can catalyse the formation of peptide bonds (Wieczorek et al. 2013), the reactions of *N*-DIPP-Ser and Ala with or without the catalysis of Ser-His were elaborately explored (Fig. 1d and **Fig. S9**). We observed that Ser-His did not substantially influence the reaction because there were similar $^{31}$P NMR integral areas of P-N products obtained from the above two reaction systems (**Fig. S9**).

Since the phosphoryl group has a strong enhancement effect on MS-based detection and can facilitate chromatographic separation due to its hydrophobicity, *N*-phosphoryl dipeptides, the precursors of dipeptide products, were selected as the observation targets to evaluate peptide bond formation efficiency by LC-MS. All the five samples in Fig. 1a incubating for approximately 6 h at 37 °C were analyzed to detect *N*-phosphoryl dipeptides by LC-MS. Comparing the five amino acids (Fig. 2), only *N*-DIPP-Ser with His can form dipeptides effectively. It should be interesting to note that *N*-DIPP-Ser-Ser-His ($Mw_{(calculation)}$ = 494.2016) could also be detected by LC-ESI-MS in the reaction system of *N*-DIPP-Ser and His (Fig. 3), with the molecule weight relative deviation of less than 5 ppm. It also indicated that *N*-DIPP-Ser-His can be produced in this system, which can be hydrolyzed subsequently and provide Ser-His to react with *N*-DIPP-Ser to form the resulting tripeptide.

In order to further verify the dipeptide formation, the precursor of Ser-His dipeptide, namely, *N*-DIPP-Ser-His, was separated from the reaction system of His with *N*-DIPP-Ser by ODS $C_{18}$ reverse phase column chromatography. The purified *N*-DIPP-Ser-His was firstly identified by HPLC-ESI-MS/MS (Fig. 4). Detailed structural information was obtained and confirmed via $^{31}$P NMR, $^{1}$H NMR, $^{13}$C NMR (**Figs. S5-S7**).

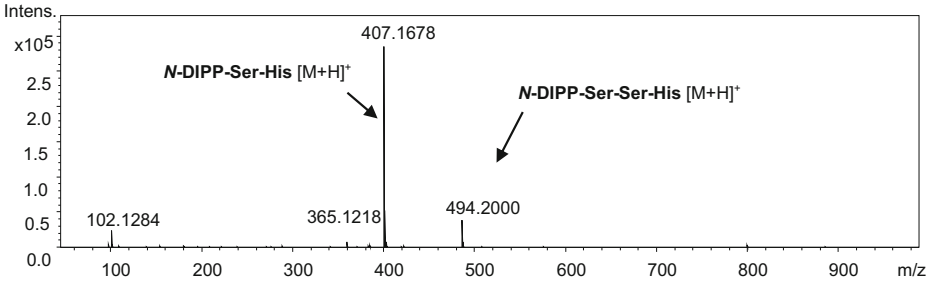



**Fig. 3** Analysis of *N*-DIPP-Ser-Ser-His by HPLC-ESI-MS

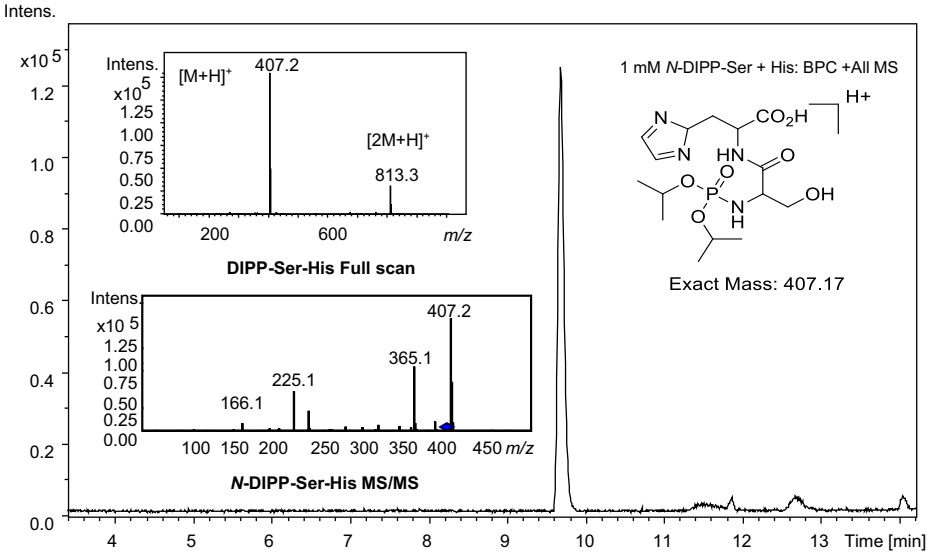



**Fig. 4** Structure identification of *N*-DIPP-Ser-His by HPLC-ESI-MS/MS. BPC is short for base peak chromatogram

To evaluate the yield of Ser-His, the internal standard method was applied in this study to calculate the yield of Ser-His according to its extracted ions chromatogram (EIC) peak area; the outcome was approximately 27% (**Fig. S10**).

The results of all peptide formation reactions above were summarized in Table 1. From Table 1, it is apparent that *N*-DIPP-Ser can effectively and selectively generate Ser-His with His.

## Differences in Dipeptide Formation among Five Amino Acids with pH Control

To further demonstrate the special selectivity of His for dipeptide formation with *N*-DIPP-Ser, the following two experiments were performed at different pH conditions. First, *N*-DIPP-Ser

**Table 1** Reaction results of *N*-DIPP-Ser with five different amino acids without pH control

| Entry No. | Reaction[a] | Products | Product Precursors ($M_{pp}$) | pH of the system | $[M_{pp}+H]^+$ | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | DIPP-Ser + Ala | Ser-Ala | DIPP-Ser-Ala | 3 | 341.15 | Trace |
| 2 | DIPP-Ser + Asp | Ser-Asp | DIPP-Ser-Asp | 3 | 385.14 | Trace |
| 3 | DIPP-Ser + Pro | Ser-Pro | DIPP-Ser-Pro | 3 | 367.16 | Trace |
| 4 | DIPP-Ser + Ser | Ser-Ser | DIPP-Ser-Ser | 3 | 357.14 | Trace |
| 5 | DIPP-Ser + His | Ser-His | DIPP-Ser-His | 6 | 407.17 | 27 [c] |
| 6 | DIPP-Ser + Ala+Imz | Ser-Ala | DIPP-Ser-Ala | 6 | 341.15 | Trace |
| 7 | DIPP-Ser + Ala+Ser-His | Ser-Ala | DIPP-Ser-Ala | 3 | 341.15 | Trace |

[a] all amino acids here are L- configuration

[b] LC-MS analysis based on the product precursor molecule ion peaks $[M_{pp}+H]^+$

[c] The quantification by LC-MS based on Ser-His molecule ion peak $[M+H]^+$ at *m/z* 243.11 (The detailed method is shown as **Fig. S10**)

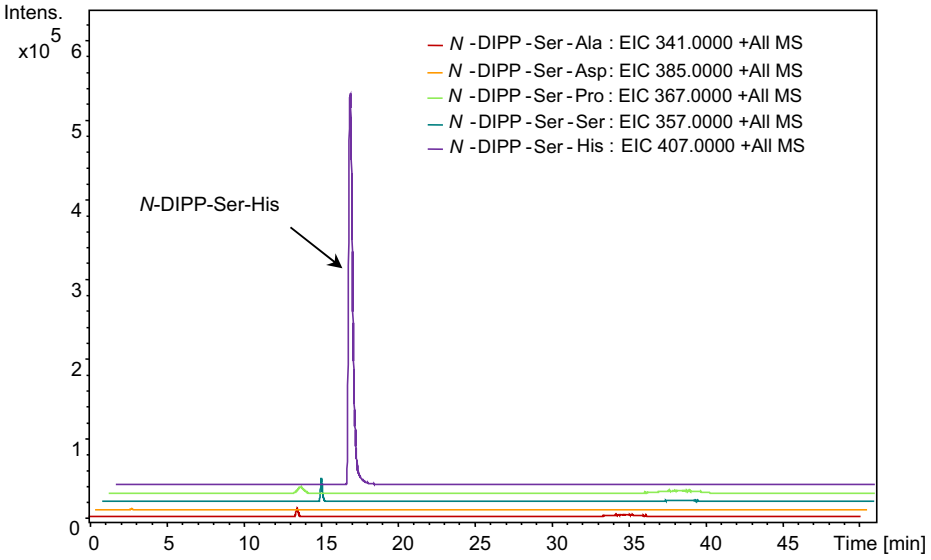



**Fig. 5** HPLC-ESI-MS results on the incubation experiments of five tested amino acids at pH 6 in imidazole system. EIC is short for extracted ion chromatogram

was incubated with all the five tested amino acids in imidazole buffer system (keeping pH at 6) at 37 °C for 24 h. The resulting products were analyzed by LC-MS. The experimental results show that only *N*-DIPP-Ser-His can be obviously detected in the reaction system (Fig. 5). This means that *N*-DIPP-Ser can react more selectively with His to form *N*-phosphoryl Ser-His than with other amino acids.

In addition, the mixture of the five amino acids was also incubated with *N*-DIPP-Ser simultaneously in aqueous solution at pH values of 3, 7, and 10 respectively, and undertakes competitive reaction experiments at 37 °C for 24 h. The experimental results (Fig. 6) show that

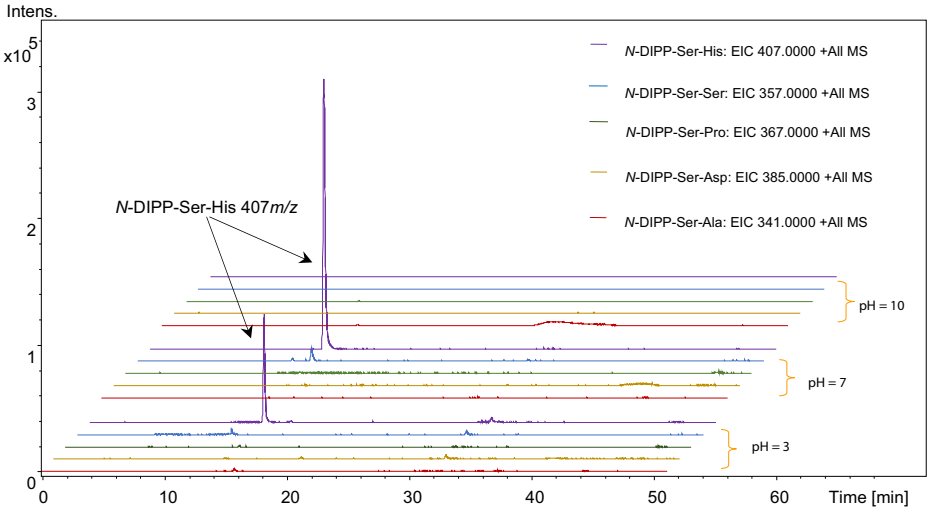
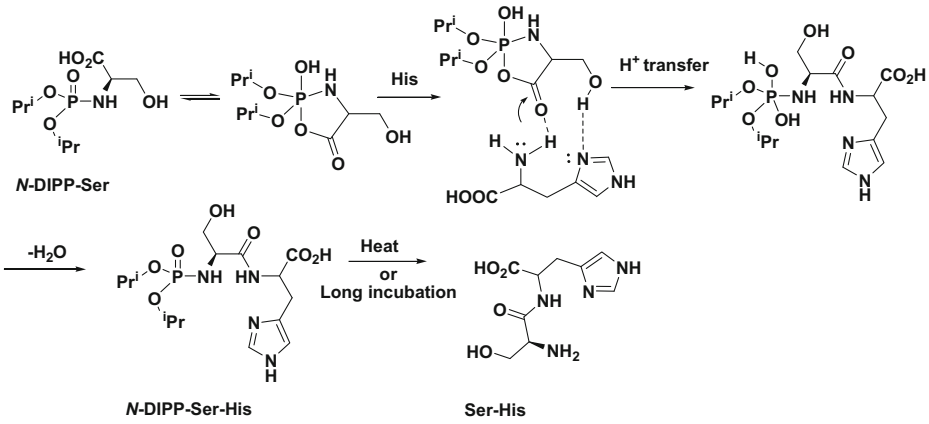



**Fig. 6** HPLC-ESI-MS results on the incubation experiments of *N*-DIPP-Ser with five tested amino acids mixtures at pH 3, 7 and 10. EIC is short for extracted ion chromatogram




**Scheme 1** Possible synergetic mechanism of Ser-His peptide formation

*N*-DIPP-Ser could form *N*-DIPP-Ser-His with His more easily and effectively than with other amino acids both at pH 3 and 7. However, no resulting derivative dipeptides were detected in the pH 10 system for all five amino acids, since *N*-DIPP-Ser is too stable in the strong alkaline condition. These results imply that Ser-His can be obtained spontaneously in the prebiotic condition because of its wide range of reaction pH .

Based on the experimental results, it can be considered that *N*-DIPP-Ser is inclined to select His or dipeptides containing His (such as Ser-His) to form dipeptides and tripeptides in weak acidic or neutral aqueous solution. The alliance of α-amino and imidazolyl groups, such as His and Ser-His, may have a synergistic effect on the formation of derivative dipeptides or tripeptides. *N*-DIPP-Ser gets close to $\alpha$ amino group of His more easily by making hydrogen bond between the imidazolyl group of His and hydroxyl group of Ser, which is beneficial for peptide bond formation of *N*-DIPP-Ser-His in the next coupling reaction step. Since the P-N bond is very labile, *N*-DIPP-Ser-His is apt to release the phosphoryl group to produce Ser-His through heating or long incubation. The possible synergetic mechanism for Ser-His dipeptide formation is shown as Scheme 1.

In conclusion, this study demonstrates that Ser and His can form Ser-His dipeptides more selectively than other ancient amino acids, such as Ala, Ser, Pro and Asp, with phosphorus activation in the aqueous phase. It implies that Ser-His could, to a certain extent, be efficiently obtained in the prebiotic chemical condition. Though the activation of peptide formation reactions reported in this study is dependent on organic phosphorus, namely, a diisopropyl phosphoryl group, all the experimental results could essentially reveal the differences among peptide formation activities of the tested amino acids. Our findings provided more evidences that Ser-His has the potential to be the candidate for the evolutionary prototype of modern hydrolase.

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**Authors contributions** Wanyun Shu and Yongfei Yu performed the main experiments involved in this paper. Wanyun Shu wrote the manuscript. Su Chen performed some NMR data analysis. Xia Yan provided us the method for the separation and purification of *N*-DIPP-Ser-His by ODS $C_{18}$ column. Yan Liu designed experiments and contributed to data analysis and interpretation as well as manuscript writing. Yufen Zhao provided the main instruments for these researches.

**Compliance with Ethical Standards**

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Approval** The article does not contain or refer to any studies with human participants or animals performed by any of the authors.

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