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Original article

Theoretical investigations on the thiol–thioester exchange steps of different thioesters

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ABSTRACT

As the rate-determining step in native chemical ligation reactions, the thiol–thioester exchange step is important in determining the efficiency of the ligations of peptides. In the present study, systematic theoretical calculations were carried out on the relationships between the structure of different thioesters and the free energy barriers of the thiol–thioester exchange step. According to the calculation results, the thiol–thioester exchange step is disfavored by the steric hindrance around the carbonyl center, while the electronic effect *(i.e.* conjugation and hyper-conjugation effects) becomes important when the steric hindrance is insignificant.

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1. Introduction

Native chemical ligation (NCL) was reported by Kent *et al.* in 1994 [1]. NCL corresponds to the formation of a polypeptide *via* the ligation of an unprotected peptide-α-thioester and an N-terminal cysteine peptide (Scheme 1). So far NCL has been widely used in chemical synthesis of proteins and peptides [2–9]. Mechanistic understandings on NCL reaction will benefit the development of more powerful strategies [10–18]. The mechanism of NCL reaction mainly consists of three steps: the thioesterification between the N-terminal Cys and C-terminal thioester, the transthioesterification on the formed thioester intermediate, and the final intramolecular S → N acyl transfer step (Scheme 2) [10–15]. With the aid of Density Functional Theory (DFT) calculation methods, we recently confirmed that the thiol–thioester exchange process is the rate determining step for thiol catalyzed NCL reactions [16,17]. To clarify the key structural parameters in NCL reaction, in the present study we carried out DFT calculations on the thiol–thioester exchange step between PhS^- and several thioesters.

2. Calculation methods

Recently, DFT calculations have been widely used in mechanistic studies of organic and bio-organic reactions [18,19]. In this paper, M06-2X/6-31G(d) [20–22] method was used for the gas-phase optimizations of all species. Frequency calculations were performed with the same method to verify the concerned compound to be minimum (with zero imaginary frequency) or transition state (with one imaginary frequency) and gain the thermal corrections to Gibbs free energy. For each transition state, IRC (intrinsic reaction coordinate) calculations were carried out to ascertain the correct connection between the transition state and the concerned reactant and product. The gas phase energies (total electronic energy with the thermal correction to Gibbs free energy) were used for all discussions unless otherwise noted. The solvent effect has also been taken into account by performing single point energy calculations (the details are given in the Supporting information). All these calculations were performed with Gaussian09 software [23].

3. Results and discussion

Six thioesters (Fig. 1) were studied and the thiol–thioester exchange step (between each of them and thiophenol anion) was examined. For clarity reasons, the transition state in the thiol–thioester exchange step and the product related to each **Cn** are named as **TS-Cn** and **P-Cn**, respectively.

We used **C1** as an example to perform detailed analysis on the structural and energetic changes in the thiol–thioester exchange step (Fig. 2). From **C1**, the approach of the thiophenol anion (PhS^-) results in the automatic lengthening of the $C\text{-}S^1$ bond, and in **TS-C1** the $C\text{-}S^1$ and $C\text{-}S^2$ bond distances are 1.991 and 2.137 Å. Thereafter, the formation of the $C\text{-}S^2$ bond compensates the energetic

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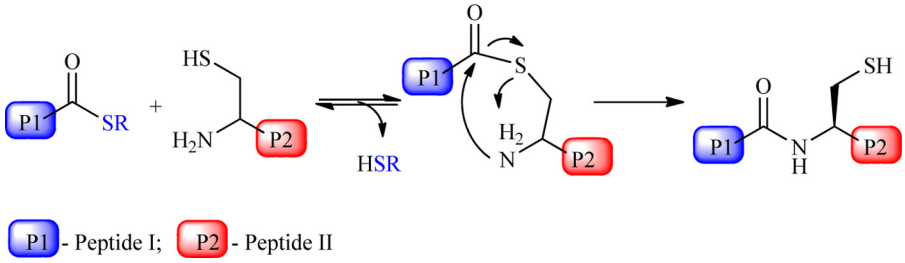
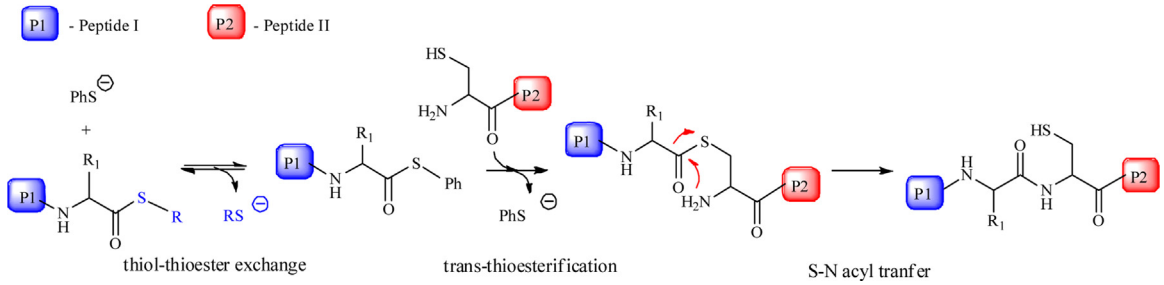


Scheme 1. Illustrative figure of NCL reaction.



Scheme 2. The proposed mechanism of thiol catalyzed NCL reaction.

necessity of the C-S^1 bond dissociation, and thus the energy becomes lower until the formation of the subsequent intermediate **P-C1**. In **P-C1**, the C-S^1 and C-S^2 bond distances are 2.056 and 2.030 Å, respectively. The C-S^2 bond distance in the separated PhS^2-connected thioester **S1** (Eq. 1 and Table 1) is only 1.810 Å. Therefore, **P-C1** retained the weak interactions between the thioester moiety and the leaving S^1R group (R = Et for **C1**). This effect weakens the interaction between the carbonyl group and the PhS^2– group, and results in the relatively longer C-S^2 bond distance in **P-C1** (than that in **S1**). The transformation of **C1** → **P-C1** is endergonic by 18.8 kcal/mol, and the activation barrier of this step is 19.8 kcal/mol (Fig. 2). Therefore, the transition state is a late-transition state. **TS-C1** is energetically and structurally close to the formed intermediate **P-C1**.

(1)

The calculation results for the other thioesters gave similar conclusions. The thiol–thioester exchange process of each thioester is endergonic, and the C-S^2 bond formation occurs with a simultaneous C-S^1 bond cleavage. All the transition states (**TS-Cn**) are late transition states, and they are structurally and energetically close to the product (**P-Cn**). The C-S^1 and C-S^2 bond distances in **P-Cn** are about 2.0 Å, indicating that C-S^1 is partially dissociated while C-S^2 is partially formed in **P-Cn** (the C-S^2 in all separated product **Sn** are all about 1.8 Å). Accordingly, in all the concerned products, the leaving S^1R group remains weakly coordinated to the carbonyl group after the thiol–thioester exchange step.

The activation barrier of different transition states varies a lot (from 3.8 kcal/mol on **C6** to 23.6 kcal/mol on **C4**). The relative free energy barriers of the aryl thioesters (**C5** and **C6**, <10 kcal/mol) are significantly lower than those of the alkyl thioesters (**C1**-**C4**, >15.0 kcal/mol), while the high energy barrier of **C4** might be originated from the steric hindrance. It is expected that the thiol–thioester exchange step will be limited by steric hindrance (disfavors the approaching of the thiol group), and therefore we examines the electronic effect of different thioesters below.

The ethyl thioester **C7** and the benzene thioester **C8** were chosen as samples to compare the electronic effect of alkyl and aromatic substituents on thioester. The substituent effect of the aromatic group on the thiol group was also examined for the comparison of the detailed electronic effect on the aromatic thiol group (**C9** and **C10** in Fig. 3). The free energy barriers of the thiol–thioester exchange step on **C7** (13.3 kcal/mol, Table 2) are higher than those on **C8**-**C10** (10.9, 11.4, and 10.3 kcal/mol). The reason is

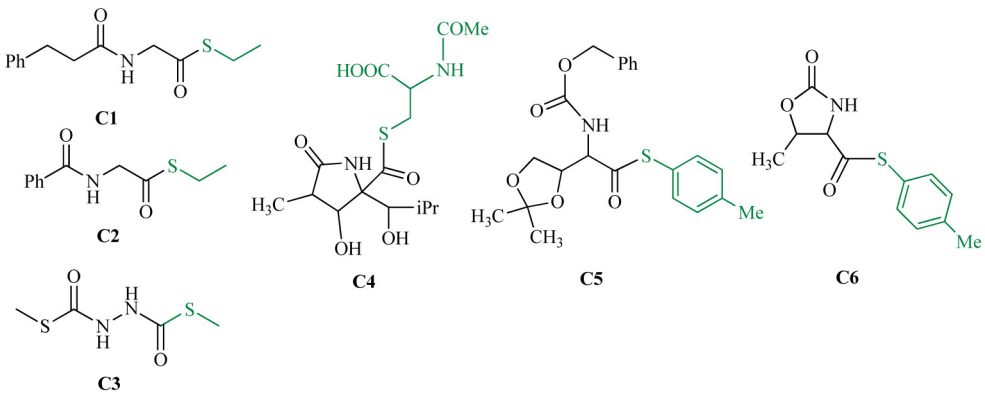


Fig. 1. The selected thioester substrates.

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