Applications of transition state calculations in the key cyclization of small molecule natural product synthesis

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Abstract. The diversification of the conformation and configuration of the carbocyclic skeleton of natural products is an important reason for the diversity and complexity of the structure of natural products. The corresponding cyclization synthesis has attracted much attention. Computational chemistry approaches have the advantages of non-toxic, harmless and relatively low cost, and they are increasingly used to model and understand molecular phenomena. The reaction mechanism and thermodynamic parameters determine the feasibility of the cyclization and the enantioselectivity of the cyclization products. The transition state calculations can provide these thermodynamic parameters, which helps to elucidate the cyclization mechanism, calculate the reaction rationality, predict the performance of the new synthesis method and provide a basis for the comprehensive synthesis design.

1 Introduction

Natural products are an important source of drugs and lead compounds as usually have unique structures and the ability to bind to specific targets. Avoiding the difficulty in extraction and separation, high cost and the ecosystem destruction, artificially synthesized natural products have gradually emerged and attracted much attention. In the early 20th century, computational chemistry approaches were introduced into the synthesis of natural products to model molecular structures and interpret experimental results. [1] With the development of computing technology, the calculation accuracy continues to improve, and the calculation model continues to diversify. Furthermore, the cost is constantly decreasing. A few decades ago, a typical transition state calculation would require months to run, in generally, while the same calculation now just takes a few seconds. [2] Appropriate calculation methods are employed to investigate various chemical and physical properties through molecular mechanics, ab initio calculations, semi-empirical and hybrid methods. [2-4] It is more and more helpful and meaningful for the comprehensive synthesis design.

Small molecules natural products with complex structures often have a carbocyclic skeleton structure, the corresponding cyclization is usually the key to synthesis. There are many conformational isomers and configurational isomers in these carbocyclic skeleton structures, [5] affected the feasibility and enantioselectivity of the cyclization, it is need to consider carefully in the synthesis design. Essentially, these isomers are a transition states or minimums on the potential energy surface, the transition state calculations can provide much information on them. Transition state

energy and thermodynamic parameters can provide important kinetic information [6] to elucidate cyclization mechanism. Transition state structure can reveal the molecular interaction that controls the chemical results, and interpret the rationality, feasibility and enantioselectivity of the synthesis. The combination of synthesis and transition state calculations is leveraged for greater understanding and guiding cyclization synthesis.

2 Elucidating mechanism and predicting reactivity: 5-exo cyclization for Chromodorolide B

The diterpenoids are a large family of natural products, which are mainly from marine sources. [7] Chromodorolide is one of the diterpenoids, and it was reported that the chromodorolides have the in vitro nematocidal, antitumor, and antimicrobial activities. [8-10] In 2018, the Overman group reported a synthesis of (-) -chromodorolide B **4** through radical cyclization cascade. [11] Moreover, they elucidated the mechanism and optimized this reaction by analysing the transition state modelling.

The reaction before optimization is shown in **Scheme 1-A**. [11] The radical cleavage of redoxactive ester compound **1** forms intermediate **2** through the 1,4-addition to (R)-5-methoxybutenolide. The intermediate **2** under-went 5-exo-trig cyclization and C–Cl cleavage to form compound **3**, and then elaborated to obtain the (-) -chromodorolide B. However, the key cyclization 5-exo cyclization is nonselective and favoured the undesirable diastereomer, namely C8 epimer **5a** (**Scheme 1-B**), resulted in the yield for the overall reaction was low.

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1-A. The route towards the synthesis of (-) - chromodorolide B before optimization.

1-B. Transition state modelling.

1-C. The route towards the synthesis of (-) -chromodorolide B after optimization.

Scheme 1. (A) The route towards the synthesis of (-) - chromodorolide B before optimization. (B) Transition state modelling. (C) The route towards the synthesis of (-) - chromodorolide B after optimization.

They came up with two possible mechanisms of transformation via 5-exo cyclization. One possible mechanism is radical mechanism, the lactone 1-radical could undergo direct 5-exo cyclization with the pendent alkene. The other one is anionic mechanism, the lactone 1-radica reduces to the lactone enolate and reacts with the allylic chloride through S_N2' . The transition state modelling was used to elucidate the cyclization mechanism, where the DFT methods are employed for the energy minimization (TPSS/def2-TZVP with BJ-damped D3-dispersion) [12,13] and single point calculation (TPPSh/def2-TZVP). The modelled result, shown in **Scheme 1-B**, indicates that it is possible for the two mechanisms thermodynamically and kinetically. Further analysis indicates that there are potential steric interactions sites that could change the reaction selectivity. If the X atom of intermediate **2** is hydrogen atom, corresponding to the radical mechanism, the 5-exo cyclization is favoured the C8 epimer. If the X atom change from hydrogen atom to the chlorine atom, the 5-exo cyclization is favoured the desired (-) - chromodorolide B, corresponding to the anionic mechanism. Furthermore, they predicted the ratio of two products. For the radical mechanism, the desired : undesired product ratio of 1 : 2.5. For the anionic mechanism, the desired : undesired product ratio of 1 : 1.3, consistent with the synthetic result. Therefore, they changed the (R)-5-methoxybutenolide to the chlorobutenolide to optimize the reaction (shown in Scheme 1-C), the optimized 5-exo-trig cyclization doesn't have the C8 epimer and the yield of chromodorolide B increases from 27% to 58%.

The Overman group successfully optimized the key cyclization in the synthesis of (-) - chromodorolide B through the transition state modelling. The potential transition state modelling approaches can elucidate mechanism and predict reactivity and guide synthetic chemists to propel their studies.

3 Understanding enantioselectivity: thioester oxy-Michael cyclization for 2,6-disubstituted THP

The 2,6-disubstituted tetrahydropyran (THP) rings are existed in a large number of structurally complex and biologically active natural products [14-18], including the lasonolide A, [19] phorbazoles, [20] psymberin [21] and diospongins [22] and so on. One usual synthesis strategy is via oxy-Michael cyclization of α,β -unsaturated carbonyl group, the products have enantioselectivity, one is 2,6-cis-diastereomers and the other one is 2,6-trans-diastereomers. Clarke group [23] reported a synthesis of utilizing thioesters as electrophiles in oxy-Michael reaction which has good enantioselectivity (**Scheme 2**). In addition, they elucidated the mechanism and enantioselectivity through the transition state calculations.

Scheme 2. The Route towards the synthesis of 2,6-cis- and 2,6-trans-THP.

TBAF and the Brønsted acid TFA are using to create a cyclization conditions respectively, the thioester substrates **6** with the 4-hydroxyl group form the 2,6-cis-THP **7** and 2,6-trans-THP **8**. Both TBAF-mediated and TFA-mediated have good selectivity. TBAF-mediated reactions mainly generated 2,6-trans-THP (2,6-cis- : 2,6-trans-THP is 20 : 1), while TFA-mediated mainly generated the 2,6-cis-THP (2,6-cis- : 2,6-trans-THP is 20 : 1). The authors guessed the cyclization mechanism and employed the MacroModel to search the possible conformation via MMFF force field, and optimized the geometries by employing the DFT with B3LYP density functional [24,25], and split-valence polarized 6-31G*+ basis set with diffuse functions. [26,27] They searched the corresponding lowest energy isomerization pathways of TBAF-mediated reaction and TFA-mediated reactions.

For TBAF-mediated cyclization, transition state calculations indicated that the active molecule is the alkoxide **9**, which attacks the conjugate double bond to form cyclizing alkoxide with 4-hydroxyl group (cyclizing 4-alkoxide **10**) and then forms 2,6-trans-THP or of 2,6-cis-THP further (**Scheme 3-A**). The forming of cyclizing 4-alkoxide has two kinds of transition state pathway (**Scheme 3-B**), consistent with 2,6-trans-THP (**TS-a**, **TS-b**, **TS-c**) and 2,6-cis-THP (**TS-d**, **TS-e**, **TS-f**) (**Scheme 3-C**). **TS-a**, **TS-b**, **TS-d** and **TS-e** are boat-like transition state, and **TS-c** and **TS-f** are chair-like. For the pathway of 2,6-trans-THP, the lowest energy structure is **TS-a** (9.1 kcal/mol relative to the active alkoxide). For the pathway of 2,6-cis-THP, the lowest energy structure is **TS-c** (10.4 kcal/mol). Since the boat-like transition state energy is relatively lower than the chair-like, the active alkoxide tends to form a cyclizing 4-alkoxide through the boat-like transition state in the buffered

TBAF mediated, which generates dominantly the 2,6-trans-THP.

For TFA-mediated cyclization, computational investigations indicated that the TFA protonates the thioester **6** to form the 1,3-TFA proton shuttle **11** and then form the 2,6-trans- and 2,6-cis-THP further (**Scheme 4-A**). For 2,6-cis-THP, the transition states have two types of conformations, namely chair-like transition state **TS-g** and boat-like transition state **TS-h** (**Scheme 4-B**). For 2,6-trans-THP, there are also two types of transition states, namely chair-like transition state **TS-i** and boat-like transition state **TS-j** (**Scheme 4-B**). Since the **TS-g** has lower energy than **TS-i** (**Scheme 4-C**), the TFA tends to protonate thioester via the chair-like transition state in the buffered TFA mediated, which forms dominantly the 2,6-cis-THP.

The Clarke group successfully provided a thioester oxy-Michael cyclization in the synthesis of 2,6-cis- and 2,6-trans-THP, the reason for the enantioselectivity was elucidated via the transition state calculations. The combination of synthesis and transition state calculations

3-A. The mechanism of TBAF-mediated cyclization.

3-B. The two kinds of pathway.

TS-a 9.1 kcal/mol TS-b 9.9 kcal/mol TS-c 19.4 kcal/mol

TS-d 10.4 kcal/mol TS-e 10.4 kcal/mol TS-f 18.7 kcal/mol

3-C. The structures of transition states.

Scheme 3. (A) The mechanism of TBAF-mediated cyclization. (B) The lowest energy pathways to the 2,6-trans **7a** (blue) and 2,6-cis **8a** (red). (C) The structures of transition states.

4-A. The mechanism of TFA-mediated cyclization.**4-B.** The two kinds of pathway.

TS-g 19.3 kcal/mol

TS-h 25.9 kcal/mol

TS-i 21.7 kcal/mol

TS-j 26.3 kcal/mol

4-C. The structures of transition states.

Scheme 4. (A) The mechanism of TFA-mediated cyclization. (B) The lowest energy pathways to the 2,6-trans **7a** (blue) and 2,6-cis **8a** (red). (C) The structures of transition states.

will be extremely useful for understanding and synthesizing functionalized THP rings with high selectivity in the context of natural product synthesis.

4 Conclusion and prospects

Transition state calculations can provide useful and meaningful insight for the key cyclization in the small molecule natural product synthesis, drive the natural product synthesis to the level of high selectivity and efficiency, and deepen the basic understanding of cyclization feasibility, reactivity and rationality.

With the development of computational technique, especially the improvement of supercomputer computing power, the system size of transition state calculation applications increases continuously, which will provide better theoretical support for the synthesis of larger and more complex natural products with carbocyclic skeleton structures and further promote the industrial production of natural product synthesis.

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