



# Computational study on the mechanism of non-catalyzed and catalyzed bromolactonization



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## ABSTRACT

Important intermediates and key transition states of catalyzed bromolactonization are researched by using density functional theory (DFT). The non-catalyzed process is also investigated to make a comparison with the catalyzed one. The pathways of reaction are investigated in detail. The results suggest that the non-catalyzed reaction proceeds in three major steps involving electrophilic addition, ring-closure and H transference, while the catalyzed process involves **Cat-NBS** interaction, H transference, and ring-closure. Electrophilic addition is the rate-determining step in the non-catalyzed process. The small discrepancy of charge density may account for the difficulty of electrophilic addition. Sulfur of **Cat** is the catalytic center which changes the charge density of Br on **NBS** to reduce the energy barrier sharply. There are four regioselective pathways related to exo-five-lactone and endo-six-lactone. The preferred pathway for exo-five-lactone is confirmed. It is the first time to uncover the catalytic mechanism by calculation method.

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## 1. Introduction

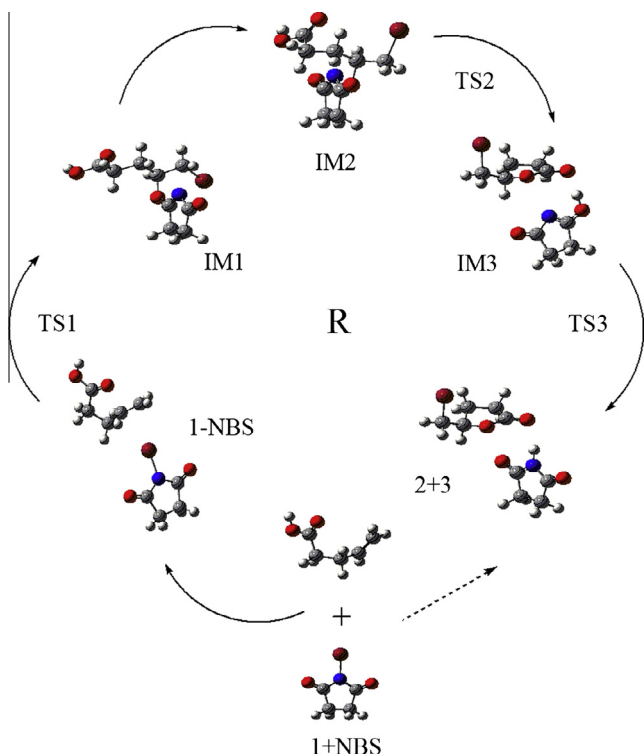
Lactones are the fundamental units of many natural products and exhibit a variety of biological activities. Compounds with the lactone ring, mainly mono- and sesquiterpenoids, are proved to be active antifeedants toward insects [1]. Lactones, such as erythromycin, aboren, acetylspiramycin, and kitasamycin are common antibiotics. Triptolide and ginkgolide are often used as the anticancer medicine [2–5]. Consequently, experimentalists show great interest in synthesizing lactones, and much attention has been focused on optimizing the experimental condition to raise the regioselectivity. Halolactonization is proved to be a versatile reaction in organic synthesis, allowing facile formation of medium ring size lactones [6]. The first reports of halolactonization introduced a way which utilized a weak base, KI, and molecular iodine for the cyclofunctionalization of unsaturated acids [7–11]. In the past decades, numerous methods were reported for the synthesis of lactones, and transition metals (Ti, Ag, Hg, Rh, Pd) or metal-complexes were used as the catalyst to promote intramolecular addition [12]. Taguchi group find that the iodocarbocyclization reaction of 4-alkenyl- or allylmalonates proceeds in good yield (96%) by treatment with I<sub>2</sub> and Ti(OR)<sub>4</sub>, the reaction temperature is almost 80 °C [13]. Ma group develop a high-yielding procedure for the synthesis of β-halobutenolides (X) (Br or I) and study Pd(0)-catalyzed

coupling reactions with terminal alkynes and organozinc reagents [14,15]. However, the utility of these methods suffers from certain drawbacks such as restricted generality, need for toxic or expensive chemicals, further resource consumption encountered in separation, etc. Then Dodd group develop a way using Copper salts and chiral ligands to promote the lactonization in mild temperature and achieves good yield (93%), 48 h is consumed to finish the reaction [16]. While high temperature or metal-based catalysts are often used to overcome the hindrance in ring closure and good yield is achieved, it is time consuming. The payment is expensive and pollute threatens the environment which are against low cost and green chemistry [17]. A method with high yield, no toxic or expensive chemicals, and mild temperature is expected.

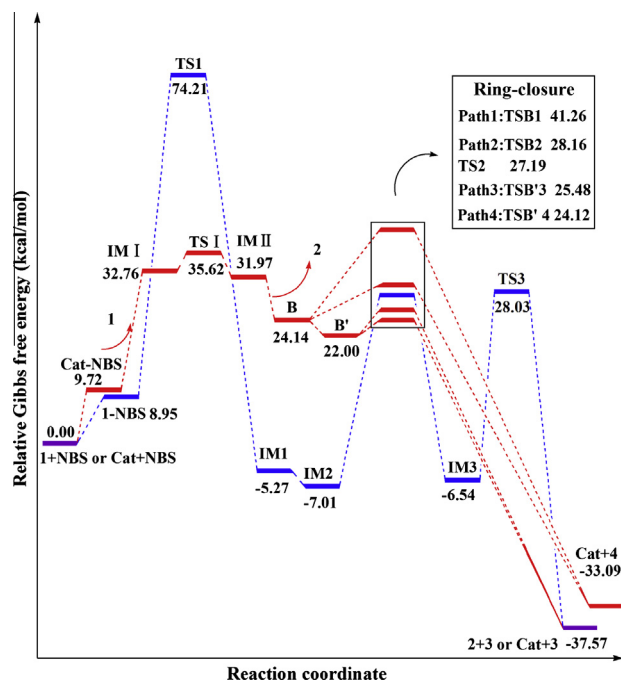
In recent years, halolactonization catalyzed by organocatalyst has received considerable attention from experimentalists and significant progress has been made in this area. Tunge introduced PhSeCl as the organocatalyst and NBS as the halogen donor to reduce the reaction time to 2 h and temperature to –30 °C [6]. Yeung group's discoveries in halolactonization have made significant achievements [18–23]. They use aminothiocarbamate and NBS to achieve 99% yield in CHCl<sub>3</sub>/toluene (1:2) at –78 °C. After that, a mild and efficient method is found to synthesize medium rings. It is consisted with a zwitterionic as catalyst and stoichiometric N-bromosuccinimide [24] as the halogen donor. 0.75 h is cost to finish the reaction with 99% yield, what's more, the reaction temperature is 0 °C which is considered as the appropriate condition. The reaction time is sharply reduced, the yield is increased and reaction temperature is easy to provide.

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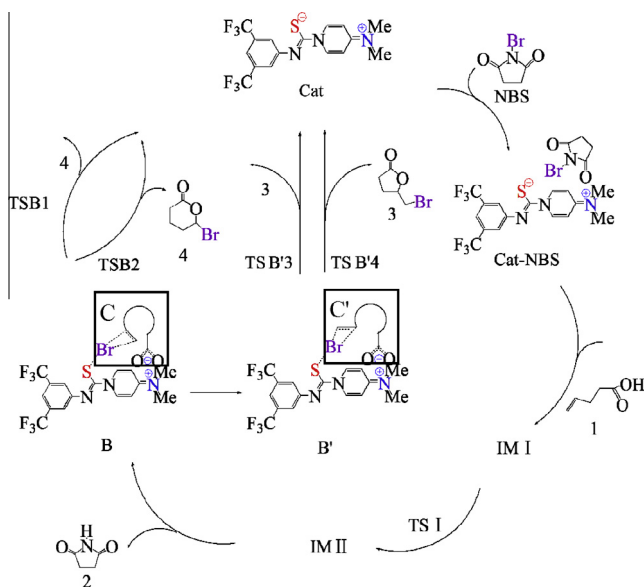
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**Scheme 1.** Proposed strategy for the bromolactonization without catalyst.

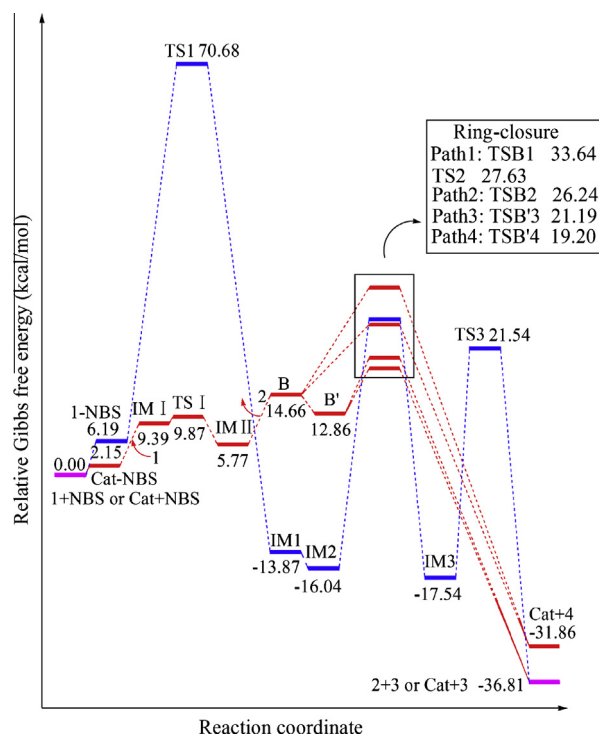


**Fig. 1a.** Relative Gibbs free energy (calculated in B3LYP method) profile of noncatalyzed (in blue) and catalyzed (in red) process of R structure in solution phase. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



**Scheme 2.** Proposed strategy of bromolactonization catalyzed by zwitterion.

Chemists have made much effort to optimize the experiment. However, unknown of the real mechanism leads to the lack of guidance for it. What is the driven force for the reaction? What is the control factor for the reaction sequence in one-pot reaction? What is the role the catalyst plays in the reaction? These questions are still to be solved. In order to understand the intrinsic mechanism of this experimental work, we herein perform a computational study of its mechanism based on density functional theory (DFT). We expect the deeper understanding of mechanism could provide guidance to improve experimental conditions and make use of organocatalyst to develop new effective ways of lactonization formation.



**Fig. 1b.** Relative Gibbs free energy (calculated in MP2 method) profile of noncatalyzed (in blue) and catalyzed (in red) process of R structure in solution phase. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

## 2. Computation details

Calculations were carried out by using the B3LYP [25–27] density functional method as implemented in the Gaussian 09 [28]

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