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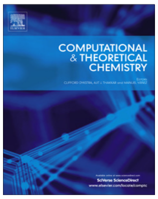

Computational study on the mechanism of uncatalyzed and selenium-based catalyzed bromolactonization

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ABSTRACT

The mechanisms of the uncatalyzed and selenium-based catalyzed bromolactonization are studied using B3LYP and MP2 method. The pathways of reaction are investigated in detail. The results suggest that the uncatalyzed reaction proceeds in three major steps involving electrophilic addition, ring-closure and hydrogen transfer, while the selenium-based catalyzed process involves **Cat-NBS** interaction, hydrogen transfer, and ring-closure. The electrophilic addition is the rate-determining step of the uncatalyzed process, while **Cat-NBS** interaction is that of the catalyzed process. Selenium of **Cat** is the catalytic center which changes the charge density of Br on **NBS**, and it makes the electrophilic addition easier. Thus, the energy barrier is sharply reduced. There are four regioselective pathways for the formation of exo-five-lactone **3** and endo-six-lactone **4**. The preferred pathway is confirmed relating to exo-five-lactone **3**.

1. Introduction

Lactones are a class of very important intermediates that are useful for many transformations in synthetic organic chemistry [1]. For example, the recently reported synthesis of C18-norditerpenoid aconitine alkaloid neofinaconitine and relay 9-deoxylappaconitine is based on ε-caprolactone [2]. Lactones have been used as folk medicines as antiarrhythmics and analgesics. Furthermore, they are not only intermediates for transformations, but also demonstrate potent antibacterial and anticancer properties [3]. For example, erythrormycin, aboren, acetylspiramycin, and kitasamycin are common antibiotics. Compounds trichorabdal A, trichorabdal B, and shikodonin inhibit tumor growth in vivo in mice, while longikaurin E, maoecristal Z and maoecrystal V exhibit in vitro cytotoxicity against several human cancer cell lines [4–8]. They are all lactones which are often used as anticancer medicines. Consequently, experimentalists show great interest in synthesizing lactones, and much attention has been focused on optimizing the experimental condition to raise the regioselectivity.

Halolactonization has been widely used in organic synthesis, especially for the preparation of molecules of biological relevance [9–11]. In the past decades, transition metals (Ti, Ag, Hg, Rh, Pd) or metal-complexes and organocatalysts are introduced to be used as the catalyst to promote intramolecular addition, and some notable successes have been recorded [12–19]. Taguchi group find that the iodocarbocyclization reaction of 4-alkenyl- or allylmalonates proceeds in good yield (96%) by treatment with I_2 and $Ti(OR)_4$, the reaction temperature is almost 80 °C [20]. Shi group introduces a procedure of bromolactonization which consists of allyl N-tosylcarbamates catalyzed by a chiral phosphine-$Sc(OTf)_3$ complex [21]. The regioselectivity and yield are great, however, the utility of these methods suffers from certain drawbacks such as restricted generality, special temperature, need for toxic or expensive chemicals, further resource consumption encountered in separation, etc. 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 [22]. Therefore, a method with high yield, no toxic or expensive chemicals, and mild temperature is expected.

Bromolactonization is a useful method of halolactonization, which is an important reaction that has been widely used in lactone synthesis due to the mild reaction conditions, high chemo- and regioselectivity, and functional group tolerance. The cheap NBS often plays the role as the bromine source. Many group has make much progress in this area. Hennecke group introduces a desymmetrization approach for asymmetric bromolactonizations of alkynes. The commercially available catalyst $(DHQD)_2PHAL$ promotes these cyclizations combined with NBS as a bromine source giving bromoenol lactones in high yield and with high enantioselectivity [23]. Yeung group also makes much effort to the

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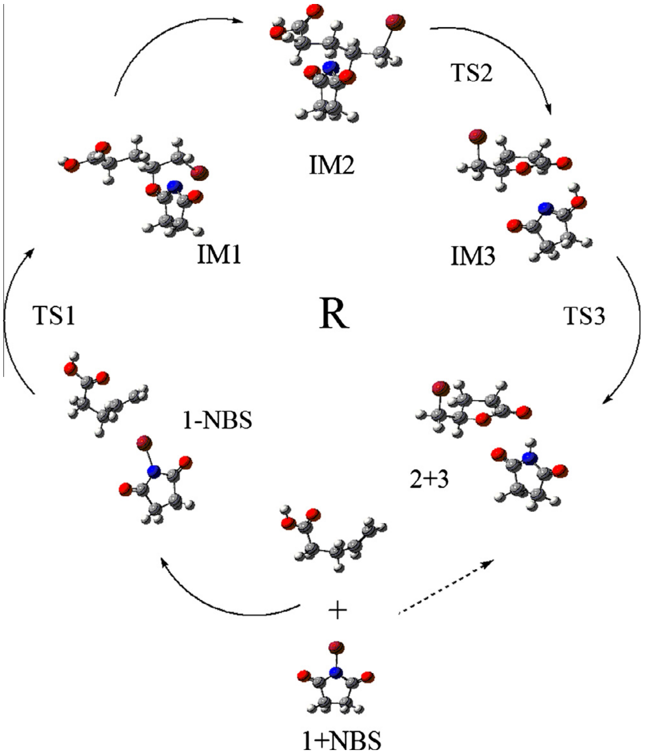
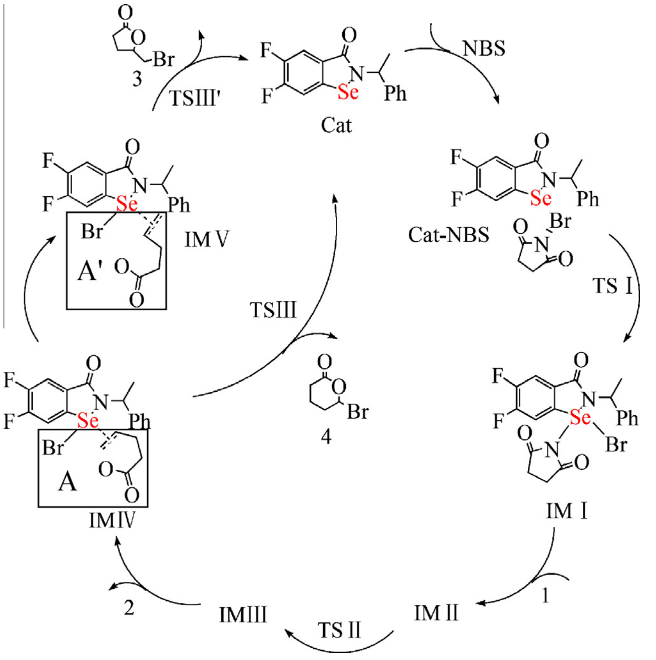


Scheme 1. Proposed strategy for the bromolactonization without catalyst.



Scheme 2. Proposed strategy of bromolactonization catalyzed by selenium-based catalyst.

bromolactonization. Series of results have been reported [12–14]. In their resent study, they mainly focus on selection of the catalyst. Sulfur-based catalyst is chosen to catalyze the bromolactonization [24]. In our previous work, the mechanism of bromolactonization catalyzed by sulfur-based catalyst has been researched by DFT method [25]. It reveals the mystic function of catalyst in the reaction.

Similarly with the sulfur-based catalyzed bromolactonization, another significant achievement is made by Kumar group [26].

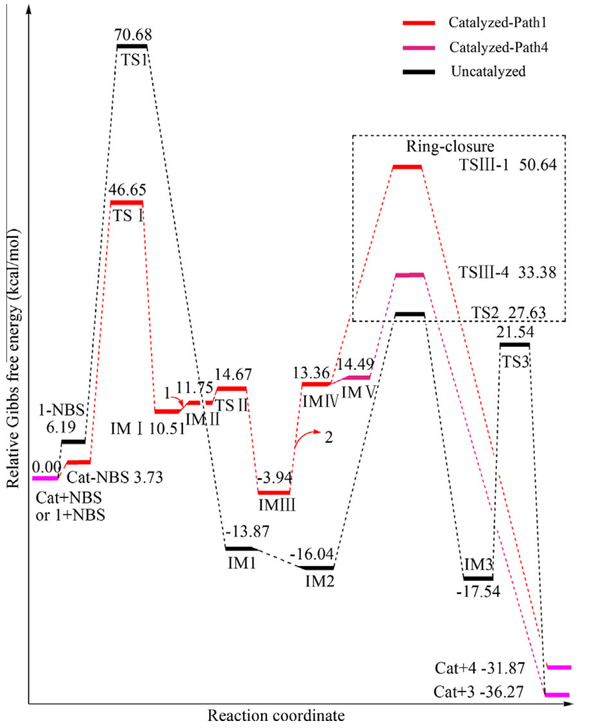


Fig. 1a. Relative Gibbs free energy (calculated in MP2 method) profile of uncatalyzed (in black) and catalyzed-path1, 4 (in red) process in solution phase. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

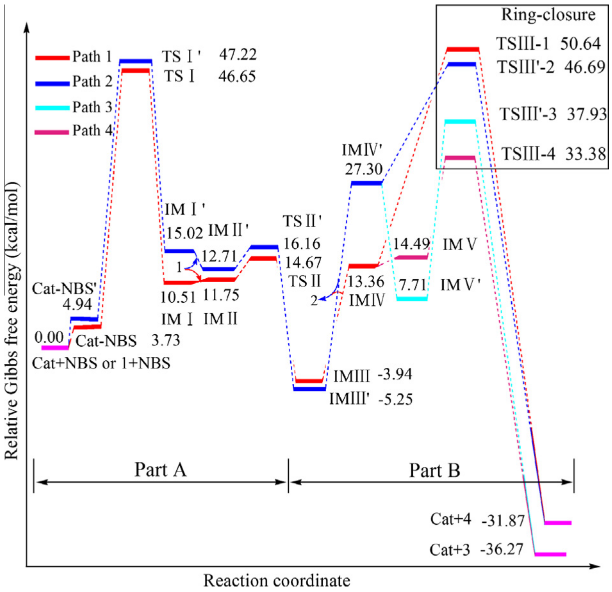


Fig. 1b. Relative Gibbs free energy (calculated in MP2 method) profile of catalyzed-path2 (in blue) and catalyzed-path1 (in red) process in solution phase. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

They develop a method using isoselenazolones as catalysts and NBS as the halogen donor in mild reaction condition. As the same main group element with sulfur, we speculate that selenium may play the similar role in the bromolactonization. In order to understand the intrinsic mechanism of this experimental work, we herein perform a computational study of its mechanism. The driven force for the reaction and the control factor for the reaction