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REGULAR ARTICLE

A DFT study on the reaction mechanisms of N-heterocyclic carbene catalyzed homodimerization of styrenes

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Abstract: In this study, the reaction mechanisms of selective tail-to-tail homodimerization of styrene catalyzed by N-heterocyclic carbene (NHC) have been firstly investigated using density functional theory (DFT). Four possible reaction channels (including the direct reaction channel and three NHC-catalyzed reaction channels) have been suggested and investigated in detail. Our calculated results indicate that one of the NHC-catalyzed channels is the most energetically favorable channel, which contains five reaction steps: the nucleophilic attack by NHC, DBU-assisted proton transfer, the dimerization, the direct [1,4]-proton transfer, and the regeneration of NHC. This work should be helpful for people to understand the dimerization at molecular level, and the novel DBU-assisted proton transfer process provides valuable insights on rational design of the suitable Brønsted acid/base catalysts for promoting this type of reaction.

AMS subject classifications: 92E99

Key words: DFT; Reaction mechanism; NHC; Homodimerization; DBU.

Introduction

Homodimerization, which means the homocoupling reaction, usually provides new industrial raw materials and valuable productions with high selectivity and high speed

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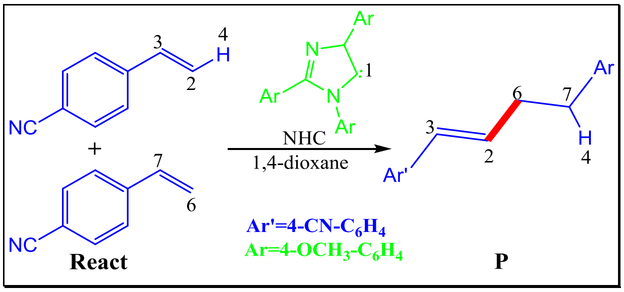
manner under the catalytic condition, and thus has attracted more and more attention over the past decades [1-3]. For example, the homodimerizational reactions include the Wurtz-Fittig reaction, the Glaser reaction, the Ullmann reaction, the Cadiot-Chodkiewicz reaction, and so on [4-7]. Although the homodimerization has been widely applied in organic chemistry, the reaction generally requires the participation of the transition metal or ion catalyst and harsh conditions, so it is highly desired to develop the green and efficient method for this kind of reaction.

In recent years, the organocatalysis is being more and more widely used in this kind of homodimerizations, which is due to the distinguishing features of low-cost and environment-friendliness [8-10]. N-heterocyclic carbine (denoted as NHC), which is famous as one of the most powerful Lewis base organocatalysts, has been found to be an ideal choice for the organic reactions [11-13]. Noteworthy, Schedler and coworkers synthesized diaryl compounds by the homocoupling reactions between two same styrenes under NHC-catalyzed condition [14], and the reaction happens at 120 ℃ in 1,4-dioxane solvent with DBU as additives (depicted in **Scheme 1**). The reaction is very convenient and attractive, but its detailed mechanism remains unclear. There are still some questions that need to be solved: What are the possible mechanisms in detail? How does NHC catalyst work? What are the roles of NHC and the additive DBU? These questions and our research interests in the NHC catalysis promote us to perform a computational study not only for obtaining a preliminary picture for the homodimerization reaction mechanism, but also for exploring the special roles of NHC and additives. We believe that the computational results should be important for understanding the organocatalysis, and thus provides valuable insights on the rational design for this kind of reactions.

In the present work, the reaction between bimolecular reactant **React** (aryl styrene) catalyzed by catalyst **NHC** to generates product **P** (diaryl styrene, depicted in **Scheme 1**), was chosen as the research object of this theoretical investigation. The detailed reaction mechanisms were studied using the density functional theory, which had been widely used on the studies of the organic [15-31] and enzymatic [32] reaction mechanisms.



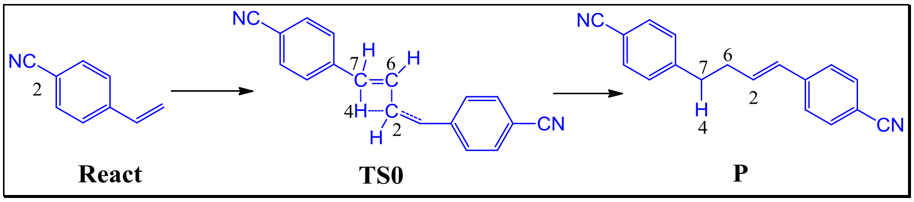
Scheme 1. The homodimerization of styrenes catalyzed by NHC

Computational details

All theoretical calculations were performed using the Gaussian 09 suite of programs [33]. All structures of the stationary points were optimized at the M06-2X/6-31G(d, p) level [34-36] in the solvent (**1,4-dioxane**), and the corresponding vibrational frequencies were calculated at the same level to take account of free energy contributions. The single-point energies of the optimized structures were then refined at the M06-2X/6-311++G(2d, 2p) [36] level with the solvent (**1,4-dioxane**) effects included and simulated by integral equation formalism polarizable continuum (**IEFPCM**) model [37, 38]. We confirmed that all the reactants, intermediates, and product have no imaginary frequencies whereas each transition state has only one imaginary frequency. The intrinsic reaction coordinate (**IRC**) [39-41] calculations were performed at the M06-2X/6-31G(d, p) level of theory to ensure that the transition states led to the expected reactants and products.

Results and discussions

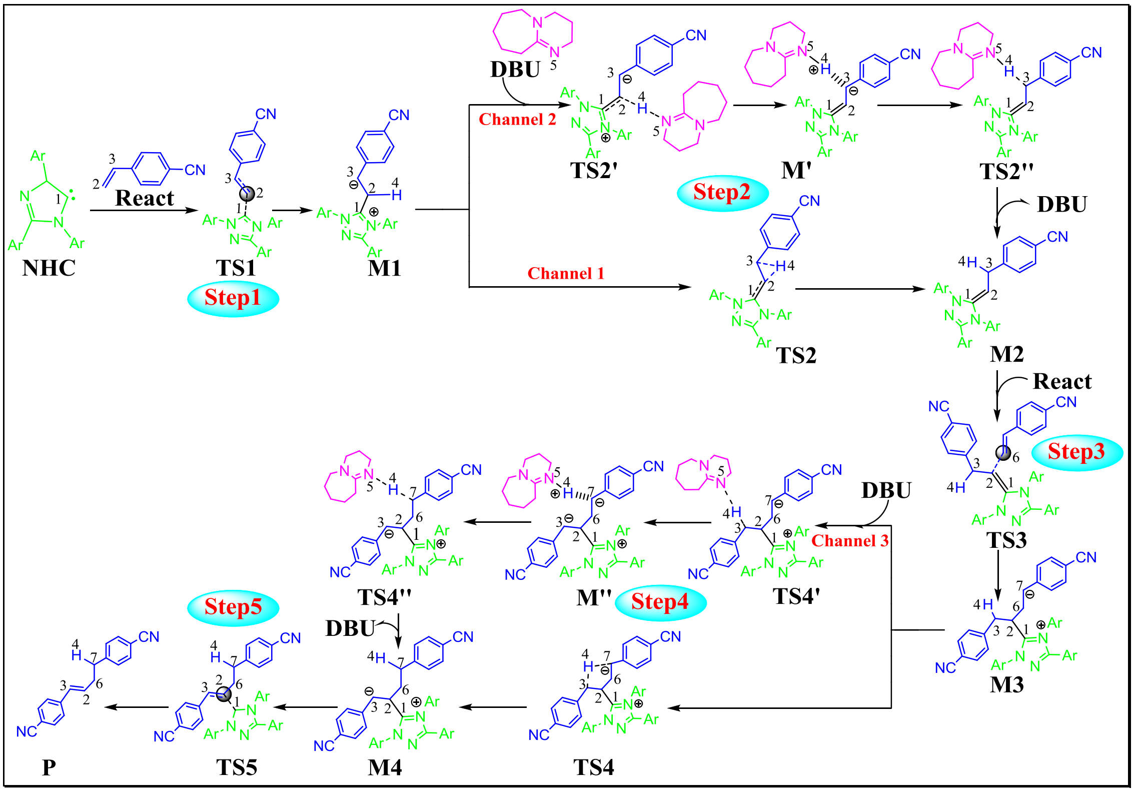
In this work, we have suggested and investigated the possible reaction mechanism of the NHC-catalyzed homocoupling reaction of styrenes. As shown in **Schemes 2** and **3**, two kinds of possible reaction mechanisms of the title reaction: (1) one is the direct homocoupling pathway, (2) the other is the NHC-catalyzed homocoupling pathways (channels 1, 2, and 3). In the following parts, we will discuss the detailed reaction mechanism of the title reaction step by step.



Scheme 2. The direct reaction channel

The Direct Reaction Pathway

We have firstly investigated the direct homocoupling reaction as depicted in **Scheme 2**, namely, two molecules of styrene react with each other to give the product via a four-membered transition state **TS0**. As shown in **Figure 1**, the homocoupling reaction occurs through the C2-C6 bond formation, which is coupled with the H4 transferring to C7. Compared to the formation of C7-H4 bond, the distances in **TS0** indicate that the formation of C2-C6 bond is slightly advanced. The Gibbs free energy of this step is 91.31 kcal/mol, demonstrating that the direct homocoupling mechanism is impossible to occur under the experimental condition.



Scheme 3. The possible reaction channels 1, 2, and 3 of NHC-catalyzed homocoupling reaction of styrenes

NHC-Catalyzed Homocoupling Pathways

As shown in **Scheme 3**, the fundamental NHC-catalyzed reaction pathway is divided into five steps: (1) the complexation process of NHC with styrenes (**React**) to form intermediate **M1**, (2) [1, 2]-proton transfer process for the formation of Breslow-type intermediate **M2**, (3) addition of the other **React** to **M2** to give intermediate **M3**, (4) [1,4]-proton transfer process for the formation of intermediate **M4**, and (5) the dissociation of NHC form the final product. As an important note, more than one possible channel involved in the second and fourth steps have been studied. **Figures 2** and **3** depict the Gibbs free energy profile and optimized structures involved in the catalytic mechanism.

Step 1: Nucleophilic addition of NHC to React. As presented in **Scheme 3**, in the first step, the C1 atom of **NHC** nucleophilically attacks on the C2 atom of **React** to forms the zwitterionic intermediate **M1** via transition state **TS1**, the optimized structures and geometrical parameters mapped in **Figure 3** show that the distance of C1-C2 shortens from 1.88 Å in transition state **TS1** to 1.52 Å in intermediate **M1**, this means that the C1–C2 bond has been formed in intermediate **M1** via transition state **TS1**. The energy barrier of this complexation process is 20.58 kcal/mol, revealing that the reaction can occur smoothly under the experimental condition.

Step 2: [1, 2]-proton transfer process. The next step is the [1, 2]-proton transfer process, in which the H4 transfers from C2 atom to C3 atom for the formation of the Breslow-type intermediate **M2**. The optimized structures and geometrical parameters mapped in **Figure 3** show that the bond length of H4-C2 increases from 1.09 Å in intermediate **M1** to 1.22 Å in transition state **TS2**, the bond length of H4-C3 shortens simultaneously from 1.42 Å of transition state **TS2** to 1.09 Å of intermediate **M2**. It means that the transfer of proton has been formed intermediate via transition state **TS2** in channel 1. As depicted in **Figure 2**, various mechanistic studies [42] show that the direct [1, 2]-proton transfer mechanism (channel 1) is impossible under mild conditions, which is due to the large strain of the three-membered ring in the transition state, our computational results also verified this fact, the Gibbs free energy in this step is very high (44.05 kcal/mol). So we suggested DBU can help the proton transfer in the other channels, the N5 atom of **DBU** attacks the H4 atom of **M1** to give intermediate **M′** (**M1′** and **DBUH)**, and then the H4 atom of **DBUH** attacks the C3 atom of **M1′** to give intermediate **M2**. The optimized structures and geometrical parameters mapped in **Figure 3** show that the distance of N5-H4 shortens from 1.27 Å to 1.05 Å, and the distance of H4-C3 from 1.60 Å to 1.10 Å, these mean that the N5-H4 bond has been formed in intermediates **M′** via transition state **TS2′**, and the H4-C3 bond has been formed in intermediate **M2** via transition state **TS2′′**. Through our computational results depicted in **Figure 2**, the Gibbs free energy barrier of the DBU-assisted proton transfer in this channel has reduced to 28.23 kcal/mol.

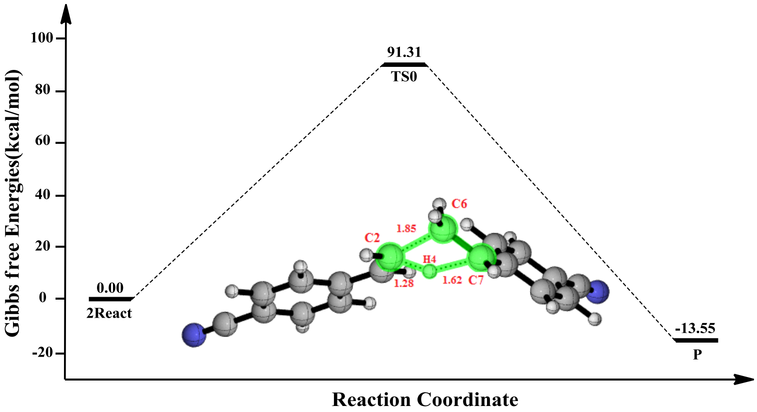


Figure 1: The Gibbs free energy profile of the direct reaction via transition state **TS0**

Step 3: Addition of the other React. As presented in **Scheme 3**, this step is that the other **React** adds to M2, i.e. the C6 atom of **React** electrophilically attacks on the C2 atom of **M2** to form the Breslow-type intermediate **M3**, and the optimized structures and geometrical parameters mapped in **Figure 3** show that the distance of C6-C2 shortens from 1.99 Å to 1.59 Å, indicating that the C6-C2 bond has been formed in intermediate **M3** via transition state **TS3**.

Step 4: [1, 4]-proton transfer process. The [1,4]-proton transfer process, in which the H4 transfers from C3 atom to C7 atom for the formation of the intermediate **M4**. The optimized structures and geometrical parameters mapped in **Figure 3** show that the distance of H4-C3 increases from 1.09 Å of intermediate **M3** to 1.48 Å of transition state **TS4** in channel 2, when the distance of H4-C7 shortens from 1.36 Å in transition state **TS4** to 1.09 Å in intermediate **M4**. The mechanistic studies [42] show that the direct [1, 4]-proton transfer mechanism is possible under mild conditions via the five-membered ring transition state, our computational results also found that the Gibbs free energy barrier of this step is 32.69 kcal/mol, which is not very high for 120 ℃. In addition, we also considered the DBU assisted proton transfer process for this step in channel 3. The N5 atom of **DBU** abstracts the H4 atom of **M3** to form intermediate **M'' (M3'** and **DBUH)**, then the H4 atom of **DBUH** transfers to the C7 atom of **M3'** to form intermediate **M4**. The optimized structures and geometrical parameters mapped in **Figure 3** show the distance of N5-H4 shortens from 1.22 Å to 1.03 Å, whereas the distance of H4-C7 from 1.56 Å to 1.09 Å, demonstrating that the N5-H4 bond has been formed in intermediate **M''** via transition state **TS4'**, and the H4-C7 bond has been formed in intermediate **M4** via transition state **TS4''**. However, the Gibbs free energy barrier of DBU-assisted [1, 4]-proton transfer (41.96 kcal/mol) in channel 3 is significantly higher than that of the direct one (channel 2), so we can exclude this reaction pathway.

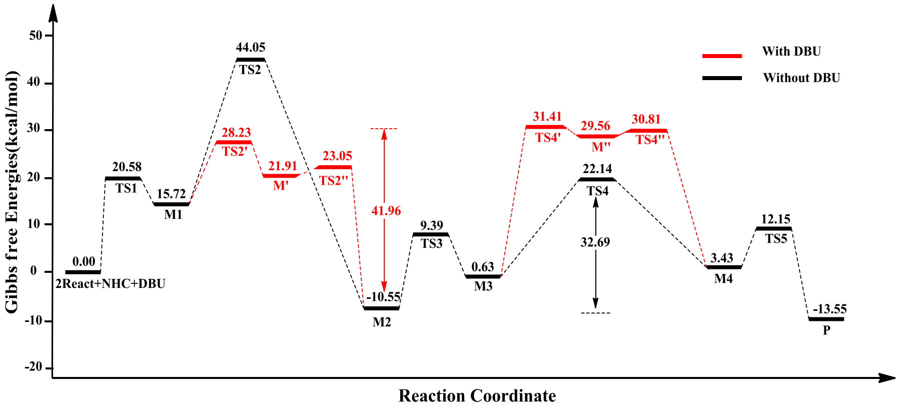


Figure 2: The Gibbs free energy profiles of the NHC-catalyzed reaction pathways

Step 5: The dissociation of NHC and product. At this step, the C1 atom of **NHC** leaves from the C2 atom of product **P**. The distance of C1-C2 increases from 1.49 Å in intermediate **M4** to 1.88 Å in transition state **TS5**.

As shown in **Figure 2**, we set the energies of the reactants (2**React**+**NHC**+**DBU**) as 0.00 kcal/mol as reference, the Gibbs free energies barriers of the five steps in the most favorable pathway (channel 2) are 20.58, 28.23, 19.94, 32.69 and 22.70 kcal/mol, and the **Step 4** is the rate-determining step.

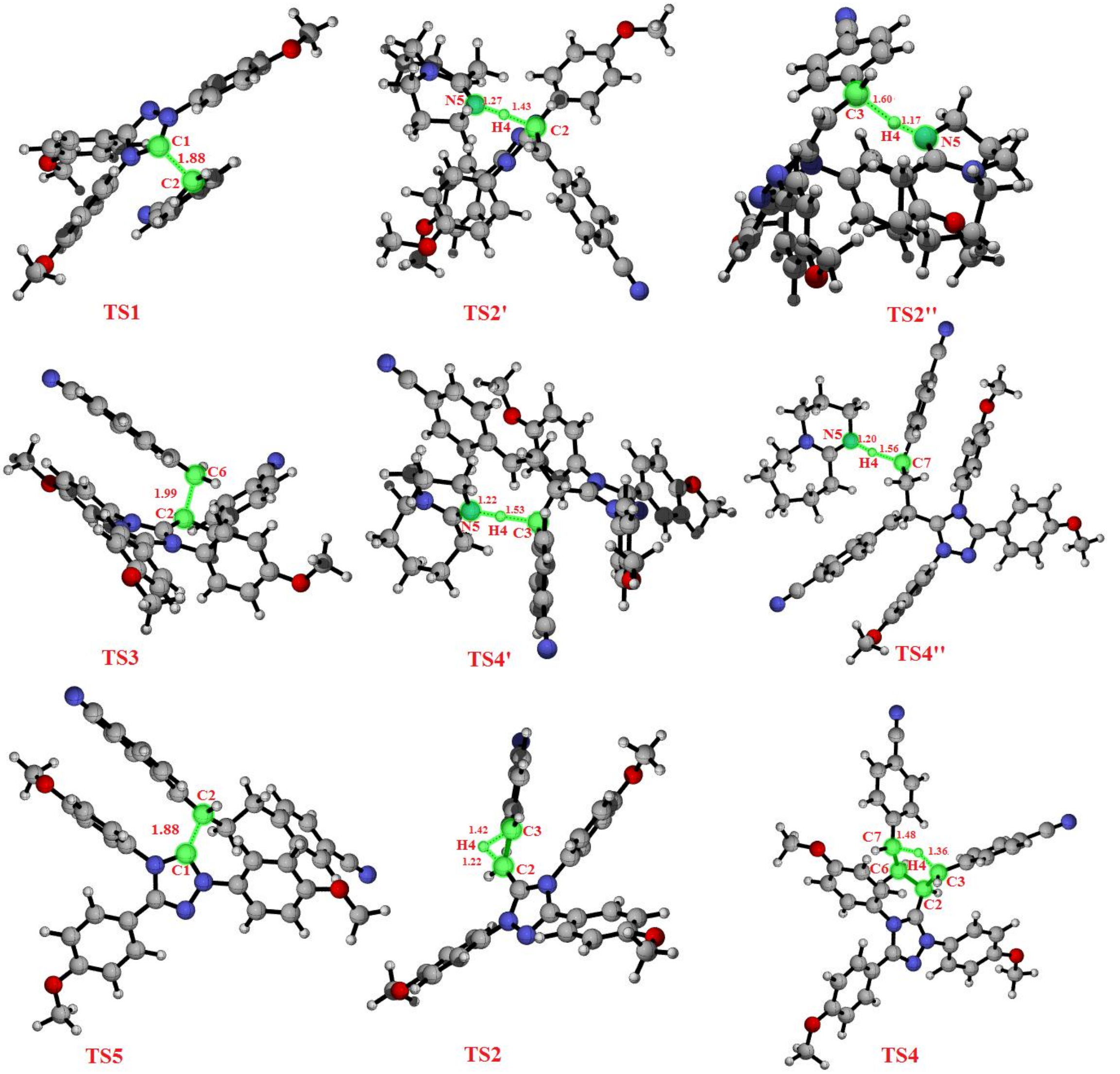


Figure 3: The optimized structures and geometrical parameters involved in the catalytic mechanism (distance in Å)

Conclusions

In this article, the possible reaction channels of N-heterocyclic carbine catalyzed selective tail-to-tail homodimerization of styrene have been investigated for the first time in theory. The energy barrier of the direct reaction is 91.31 kcal/mol, indicating that it cannot happen under mild condition, and the reaction seems to only can happen with the presence of NHC catalyst. Moreover, NHC as an organocatalyst has played an important role, and additive DBU works as Brønsted acid/base to assist the [1, 2]-proton transfer rather than the [1, 4]-proton transfer. Finally, the energy barriers of the rate-determining steps in the NHC-catalyzed channels 1, 2, and 3 are 41.96, 32.69, and 44.05 kcal/mol, respectively, which demonstrates that the channel 2 should be the most energy favorable channel and can occur easily at the heating condition (about 120 ℃). In this reaction, the reactivity of **React** is improved through the nucleophilic attack of **NHC**, however, the proton transfer is still very diffcult to happen without base DBU. Thus, both Lewis base catalyst NHC and DBU are necessary for this kind of reactions, and chemists can replace NHC by other Lewis bases such as amine and organophosphine, which can also cooperate well with base DBU. As concerned as above, this work would provide some valuable insights into the rational design of cooperatively organocatalysis for this kind of reaction.

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