

Theoretical Study of N-Heterocyclic Carbenes-Catalyzed Cascade Annulation of Benzodienones and Enals

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ABSTRACT Growing attention in developing new N-heterocyclic carbene (NHC)-mediated reactions involving homoenolate intermediates has prompted our interest in exploring the mechanistic details of the related reactions. In this work, we carried out a detailed theoretical study for the NHC-catalyzed annulation reaction of cinnamaldehyde (**A**) and benzodi(enone) (**B**) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). By performing density functional theory calculations, we show clearly the detailed reaction mechanism and rationalize the experimental observation. The reaction of **A** and **B** falls into two stages: the formation of homoenolate intermediate and the annulation of homoenolate with **B**. In the homoenolate formation stage, three possible paths are characterized. The pathway involving the DBU-assisted 1,2-proton transfer with a stepwise mechanism is kinetically more favorable, and the DBU-assisted C1 proton departure is the rate-determining step of the total reaction. The annulation of homoenolate with **B** involves four elementary steps. The conformational difference of homoenolate (*cis* and *trans*) leads to two slightly different reaction processes. In the total reaction, the process involving *cis*-conformation of **A** is kinetically more feasible. This can be clearly understood through the frontier molecular orbital analysis and the electronic inductive effect. The calculated results are expected to offer valuable information for further design and development of NHC-mediated reactions. *Chirality* 25:521–528, 2013. © 2013 Wiley Periodicals, Inc.

KEY WORDS: N-heterocyclic carbenes; homoenolate intermediates; annulation reaction

INTRODUCTION

In recent years, N-heterocyclic carbenes (NHCs) as organocatalysts have been attracting more and more attention.^{1–8} This is largely attributed to one fascinating character of NHCs, which can induce the umpolung of carbonyl compounds to yield the “Breslow intermediate,”^{9–11} and hence offers easy access to some desired molecules by undergoing Benzoin condensation, Stetter reaction, and so on. Currently, a great deal of effort in the field of organocatalysis has been devoted to the development of new NHC-catalyzed reactions.

Recently, Burstein and Glorius¹² and Bode and colleagues¹³ reported for the first time that the addition of NHC to enals can effectively lead to the direct formation of homoenolates^{14–16} with an anionic β -C atom to a carbonyl group, which can serve as ideal nucleophiles for catalytic conjugate additions. The discovery opens up new opportunities for the development of NHC-mediated transformations. To date, it is widely accepted that homoenolates can act as a powerful three-carbon synthon for the generation of various unconventional C-C and C-N bonds, and many new reactions involving homoenolate intermediates via NHC catalysis have been developed.^{17–22} The details related to the synthetic applications of homoenolate intermediates have been collected and summarized in the tutorial reviews by Nair et al. in 2008⁶ and 2011,² respectively. Despite growing interest in exploring new reactions involving homoenolate intermediates via NHC catalysis, only a few studies^{23,24} have been done to characterize the mechanistic details of the related reactions. This lack will be unfavorable to further design and development of NHC-catalyzed transformations. Therefore, an

explicit understanding of the micromechanism of NHC-mediated reactions is highly desired.

In 2011, Chi and colleagues²⁵ reported a new annulation reaction of enals and di(enone)s mediated by NHC in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which, surprisingly, leads to the generation of benzotricyclic products containing four stereocenters with exceptionally high regio- and stereoselectivities (see product **C** in Scheme 1) rather than the expected cyclopentene derivatives. To better explain the observed phenomena, a reaction mechanism was postulated by Chi and colleagues, as shown in Scheme 1. However, the details of the mechanism are still ambiguous and worthy of further exploration. It is necessary to carry out a detailed mechanistic investigation to complement the experimental study and rationalize the experimental observations. In this work, we used the density functional theory (DFT) method^{26–29} to investigate the details of the mechanism for the annulation reaction of enals and di(enone)s mediated by NHCs in the presence of DBU. The calculated results are

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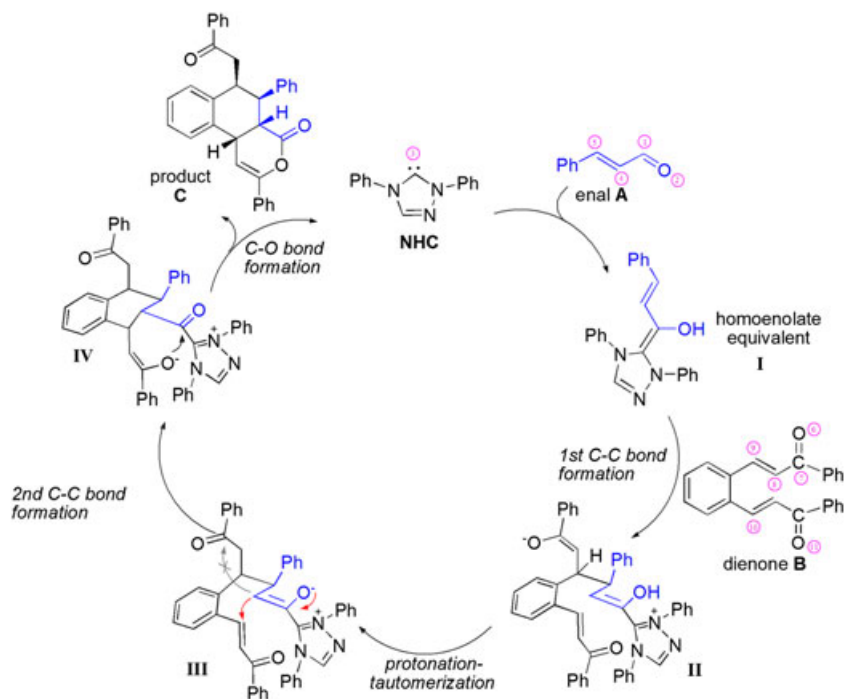
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Scheme 1. Postulated catalytic pathways for NHC-mediated annulation of cinnamaldehyde and benzodi(enone) by experiment.²⁵

expected to shed light on the experimental observations and offer the valuable information for further design and development of NHC-mediated reactions.

MATERIALS AND METHODS

As shown in Scheme 1, we chose the annulation reaction of cinnamaldehyde and benzodi(enone) catalyzed by 1,3-diphenyltriazolium-based NHC in the presence of DBU as a model reaction. For the sake of convenience and clarity, cinnamaldehyde, benzodi(enone), product and 1,3-diphenyltriazolium-based NHC will be denoted **A**, **B**, **C**, and **NHC**. Furthermore, two different conformations of **A** (*cis* and *trans*, denoted as **A^C** and **A^T**) are considered in our calculations, which lead to two slightly different pathways. The corresponding intermediates (**IM**) and transition states (**TS**) are differentiated by superscript **C** and **T**, respectively.

Considering the complexity of the theoretical model used for this study, our calculations were carried out at the B3LYP/6-31G(d) levels by including the dielectric solvent effect of tetrahydrofuran (THF), which was taken into account using a simple self-consistent reaction field (SCRF) method,^{30,31} based on the polarizable continuum model (PCM).^{32,33} The dielectric constant of THF was taken as 7.58. All of the structures (local minima or first-order saddle points) were located by performing full geometry optimization without any symmetric restriction, and their natures were characterized by performing frequency calculations, from which the zero-point energies (ZPEs) were also derived. Intrinsic reaction coordinate (IRC) calculations were performed to verify that each saddle point links two desired minima. The atomic charge assignments were based on the natural population analysis (NPA). For all cited energies, the ZPE corrections are included. All calculations were performed using Gaussian 09 program package.³⁴

RESULTS AND DISCUSSION

In our calculations, the mechanism proposed by Chi and colleagues²⁵ is considered a preliminary clue for the present theoretical study. As shown in Scheme 1, the key homoenolate equivalent **I** is firstly generated by nucleophilic attack of **NHC** to **A** followed by a proton shift. Then, a Michael addition

occurs between **I** and **B** to form intermediate **II**, which undergoes a proton transfer to afford intermediate **III**. Finally, intramolecular addition of **III** regenerates the catalyst **NHC** and furnishes the final product **C** via intermediate **IV**. In order to facilitate discussion, the whole process is divided into two stages: the formation of homoenolate intermediate and the annulation of homoenolate intermediate with **B**. The corresponding potential energy surface (PES) profiles with the optimized geometries are depicted in Figures 1, 2, 3, and 4, where the sum of the energies of the isolate reactants (**A^T** or **A^T** + **B**) and catalyst **NHC** is taken as zero energy. the numbering system of atoms is shown in Scheme 1.

The Formation of Homoenolate Intermediate

The formation of homoenolate intermediate as the first stage of this catalytic reaction has been previously studied by performing quantum chemistry calculations,^{35–37} and is considered generally to consist of two elementary steps (see path I (**IM1** → **IM2** → **I**) in Scheme 2). First, **NHC** nucleophilically attacks C1 atom of **A** to form the zwitterionic intermediate **IM2**, and then a 1,2-proton shift from the zwitterionic intermediate **IM2** occurs to afford the homoenolate intermediate **I**. However, it is indicated in recent theoretical studies^{23,24,38,39} that the direct 1,2-proton transfer needs to overcome a very high energy barrier due to the large strain in the three-membered transition state, and thus is unfeasible. This is consistent with our calculated outcomes. As shown by path I in Figure 1, the nucleophilic attack of **NHC** to **A** (TS_{1-2}^C and TS_{1-2}^T in Fig. 2) involves barriers of only about 12–15 kcal mol^{−1} with respect to the isolate reactants (**A^T** + **NHC**), while the energies for the direct 1,2-proton shift (TS_{2-1}^C and TS_{2-1}^T in Fig. 2) are found to be as high as 47–55 kcal mol^{−1}, indicating that the direct formation of the homoenolate intermediates **I^C** and **I^T** from the zwitterionic intermediates **IM₂^C** and **IM₂^T** is kinetically unfavorable.

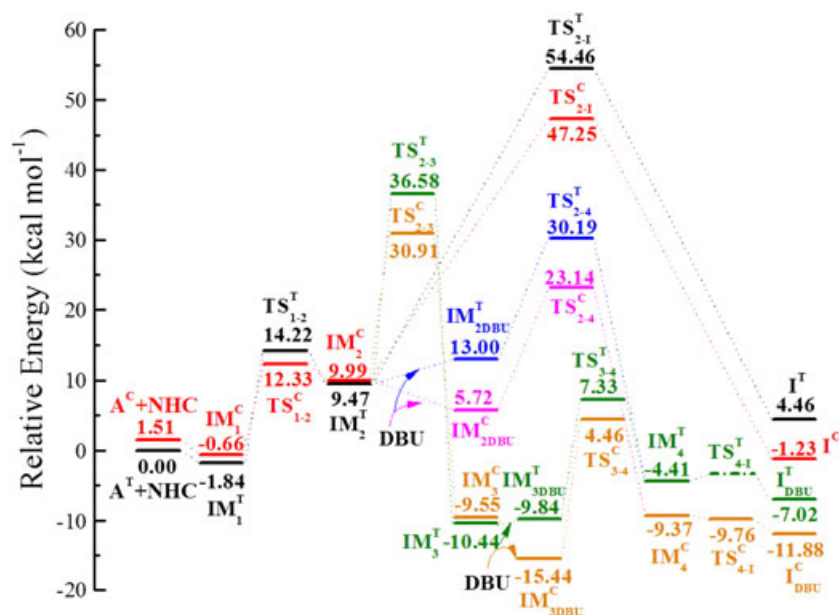


Fig. 1. Potential energy surface profiles for the generation of homoenolate equivalent (**I**) from **A^C**, **A^T** and **NHC** along paths I (black and red lines), II (green and orange lines) and III (blue and pink lines).

In 2011, Sunoj and colleagues²⁴ reported the formation mechanism of homoenolate intermediate in the presence of DBU, where a 1,3-proton transfer and a following

DBU-assisted 2,3-proton shift (see **IM1** → **IM2** → **IM3** → **I** in Scheme 2) are kinetically preferred to the direct 1,2-proton transfer for yielding homoenolate intermediate **I**. On this basis, we studied the 1,3-proton transfer and 2,3-proton shift processes of the zwitterionic intermediates **IM₂^C** and **IM₂^T** in the presence of DBU, which is denoted path II. The nucleophilic attack of **NHC** to **A** will be not taken into account again because they have been discussed above. The corresponding PES profiles are depicted in Figure 1 and the optimized geometries of transition states and intermediates are shown in Figure 2 and Supporting Figure S1, respectively. Transition states **TS₂₋₃^C** and **TS₂₋₃^T** correspond to the 1,3-proton transfer from the zwitterionic intermediates **IM₂^C** and **IM₂^T**, which lie above the isolated reactants by 31.91 and 36.58 kcal mol⁻¹, respectively. The forward IRC calculations from **TS₂₋₃^C**/**TS₂₋₃^T** demonstrate that intermediates **IM₃^C**/**IM₃^T** are on the product sides of the first-order saddle points. When DBU enters into the reaction system, two new complexes, **IM₃^C_{DBU}** and **IM₃^T_{DBU}**, are formed via H-bond interactions between **IM₃^C**/**IM₃^T** and DBU (see Supporting Fig. S1). From intermediates **IM₃^C_{DBU}** and **IM₃^T_{DBU}**, the DBU-assisted 2,3-proton shift occurs. It should be noted that the DBU-assisted 2,3-proton shift in our calculations involves a stepwise mechanism, which is distinct from the concerted mechanism reported by Sunoj and colleagues.²⁴ As shown in Scheme 2, the C3 protons of **IM₃^C_{DBU}** and **IM₃^T_{DBU}** are first deprived by DBU to form intermediates **IM₄^C** and **IM₄^T** via transition states **TS₃₋₄^C** and **TS₃₋₄^T**, lying only 4.46 and 7.33 kcal mol⁻¹ higher in energy than the separated reactants. Then, the protons abstracted by DBU will be delivered to O2 atom via **TS_{4-I}^C** and **TS_{4-I}^T** to generate the homoenolate intermediates **I_{DBU}^C** and **I_{DBU}^T**. However, we only locate the transition state **TS_{4-I}^C**, which is slightly lower than **IM₄^C** by 0.39 kcal mol⁻¹, but is 1.90 kcal mol⁻¹ higher than **IM₄^C** in electronic energy. This can be attributed to the harmonic approximation for the vibrational conditions. Although **TS_{4-I}^T** was not located in the present work, it is expected to also have a low barrier, like

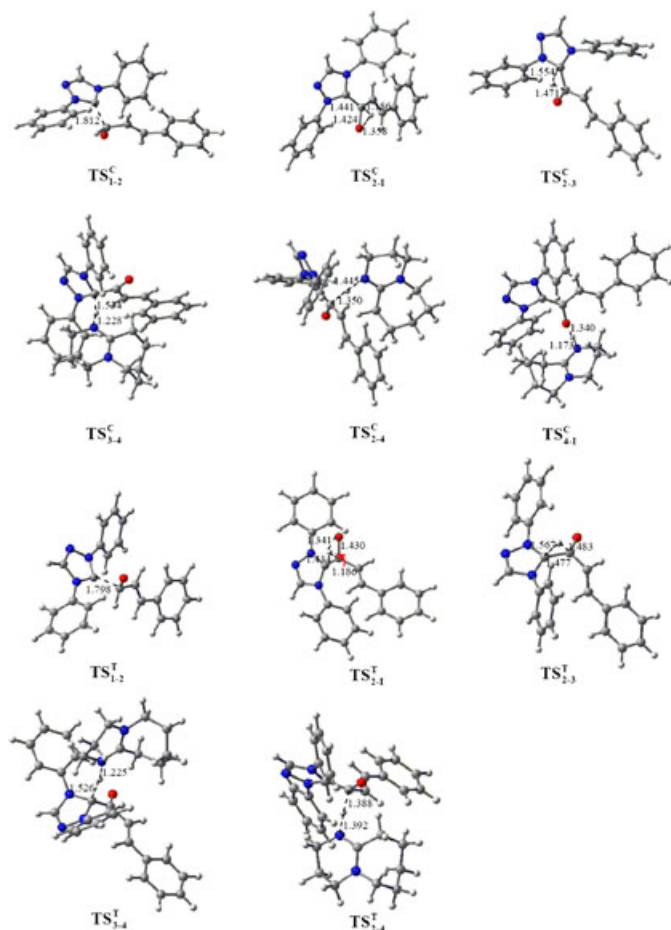


Fig. 2. Optimized geometries of transition states on the potential energy surface profiles for the generation of homoenolate equivalent (**I**) from **A^C**/**A^T** and **NHC** along paths I, II and III. The distances are in Å.

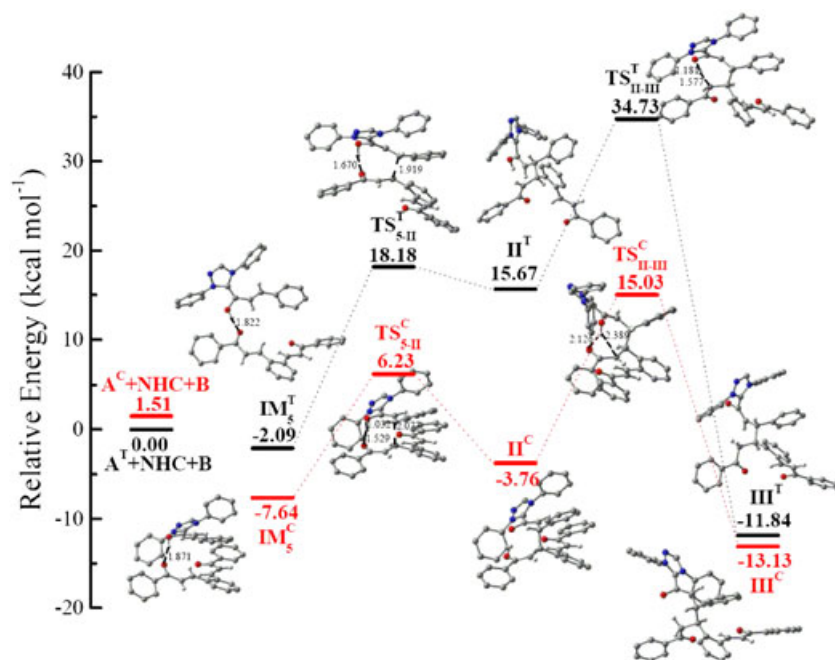


Fig. 3. Potential energy surface profiles with the optimized geometries for the addition reaction of homoenolate equivalent **I** (**I**^T and **I**^C) and dienone **B** to form intermediate **III** (**III**^T and **III**^C). The hydrogen atoms, except for those on C=C bonds and O atoms, are omitted for clarity. The distances are in Å.

TS_{4-7}^C . As stated above, the rate-determining steps in path II are the 1,3-proton transfer processes with barriers of 30.91 and 36.58 kcal mol⁻¹ with respect to the isolated reactants, which are less energy-demanding by 16–18 kcal mol⁻¹ than the direct 1,2-proton transfers. This fact indicates that path II for our computational model is more kinetically feasible than path I, consistent with Sunoj and colleague's report.²⁴

In spite of the obvious superiority of path II rather than path I, our calculations propose a more energetically favorable path III (Scheme 2), in which a DBU-assisted 1,2-proton shift with a two-step mechanism is found to present a lower energy cost

than the direct 1,2-proton transfer in path I and even the 1,3-proton shift in path II. As shown in Figures 1, 2, and Supporting Figure S1, IM_2^C/IM_2^T directly miss the C1 proton with the help of DBU to form intermediates IM_4^C/IM_4^T after the nucleophilic additions of NHC to **A**. The steps proceed via transition states TS_{3-4}^C/TS_{3-4}^T with barriers of 23.14/30.19 kcal mol⁻¹, and are the rate-determining steps in path III. The following processes to obtain the homoenolate intermediates I_{DBU}^C/I_{DBU}^T are the same with path II, and thus will not be discussed again. From Figure 1, it is clear that the DBU-assisted C1 proton leaving is lower by 6–8 kcal mol⁻¹ in energy than the 1,3-proton shift in

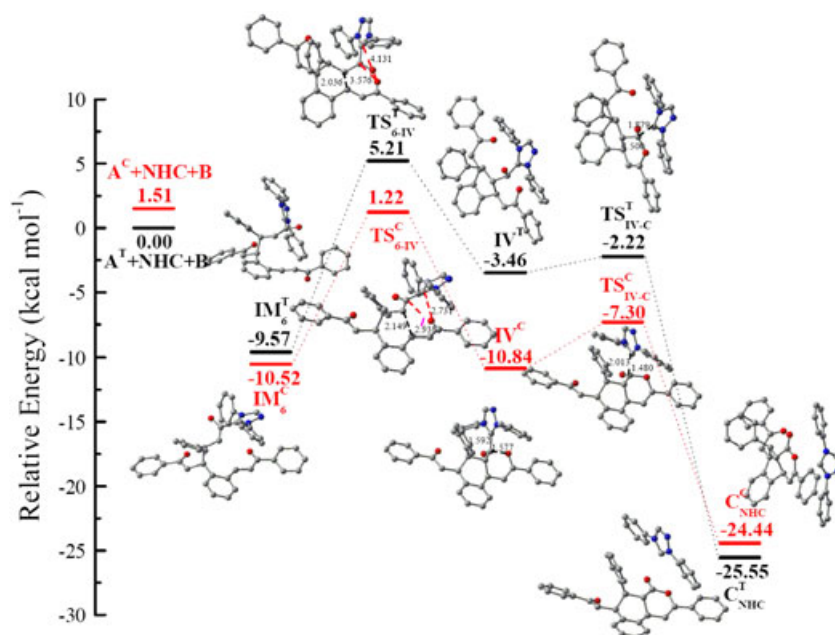
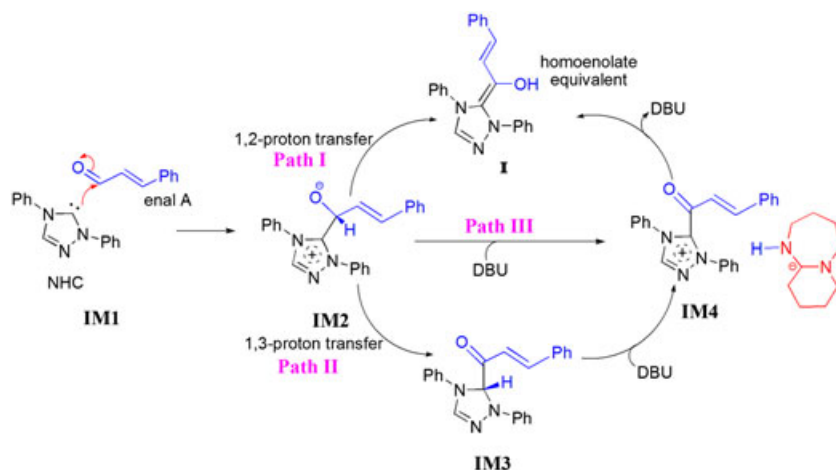


Fig. 4. Potential energy surface profiles with the optimized geometries for the reactions from intermediate **III** (**III**^T and **III**^C) to product **C**. The hydrogen atoms are omitted for clarity. The distances are in Å.



Scheme 2. Possible mechanisms for the generation of homoenolate intermediate (**I**) from **A** and NHC.

path II, indicating that path III found by us is the most feasible for the formation of a homoenolate intermediate in the presence of DBU.

Through the above analyses, we also find that the homoenolate formation process involving A^C is more favorable than that involving A^T , although A^T is more stable by 1.51 kcal mol⁻¹ than A^C . This fact can be easily understood by performing a frontier molecular orbital (FMO) analysis. It is generally known that the reactivity between two molecules is inversely proportional to the energy difference between the highest occupied molecular orbital (HOMO) (the lowest unoccupied molecular orbital [LUMO]) of one molecule and the LUMO (HOMO) of the other. The smaller the HOMO-LUMO difference is, the more reactive the reaction is. As shown in Figure 5a, the reaction between **A** and NHC proceeds via the $HOMO_{NHC}-LUMO_A$ interaction, and the $HOMO_{NHC}-LUMO_{A^C}$ difference is smaller than the $HOMO_{NHC}-LUMO_{A^T}$ difference, implying that A^C is more reactive than A^T . This explains the above theoretical observations.

The Annulation of Homoenolate Intermediate With Di(enone)

The generation of homoenolate intermediate **I** initiates the following cascade annulation reaction between **I** and **B**, the second stage of the catalytic reaction. It should be noted that our specific attention was focused on understanding the mechanism details of the NHC-catalyzed cascade annulation of di(enone)s and enals. Therefore, investigations concerning the stereoselectivities will be not considered in this work.

Figure 3 shows the PES profiles for the addition reaction of homoenolate equivalent **I** (I^C and I^T) with **B** to form intermediate **III** (III^C and III^T). The calculated results reveal that the conformational difference of I^C and I^T leads to two different reaction processes. Starting from IM_5^C , the complex of **B** and I^C , the nucleophilic addition of I^C to **B** occurs with a concomitant hydrogen transfer from the O2 atom of I^C to the carbonyl O6 atom of **B** to form intermediate II^C , which is accompanied by a small energy release of 3.76 kcal mol⁻¹. This step is in agreement with the previous theoretical studies^{23,24} on the addition reactions of homoenolate intermediates to enones. The conversion of IM_5^C to II^C proceeds via transition state TS_{5-II}^C , which is located at 6.23 kcal mol⁻¹

higher than the isolated reactants ($A^T + NHC + B$). Along the reaction coordinate, III^C can be directly obtained from II^C via transition state TS_{II-III}^C , where the proton on the carbonyl O6 atom is migrating to the C8 atom with the aid of the carbonyl O2 atom, as indicated by the calculated geometrical parameters and the vibrational mode of the imaginary frequency of TS_{II-III}^C . The energy of TS_{II-III}^C is calculated to be 15.03 kcal mol⁻¹ relative to the initial reactants, which can be reduced in the presence of DBU, as indicated by Sunoj and colleagues,²⁴ despite that the corresponding transition state is not located in our calculation. The whole process is exothermic by 13.13 kcal mol⁻¹. Next, we consider the addition process of I^T with **B**. The reaction starts from a precursor IM_5^T , in which the H-bond interaction holds I^T and **B** together to release a small energy of 2.09 kcal mol⁻¹. Then the nucleophilic addition of I^T to **B** occurs via transition state TS_{5-II}^T to generate intermediate II^T . It should be noted that TS_{5-II}^T differing from TS_{5-II}^C does not involve the hydrogen transfer from the O2 atom of I^C to the carbonyl O6 atom of **B**. This can be understood in terms of an electronic inductive effect. As shown in Figure 5b, the C5 atom in I^C carries more negative charge than that in I^T . As the C5 atom in **I** and C9 atom in **B** approach each other during the addition reaction process, more positive charge is centered on the C9 atom in TS_{5-II}^C (see Table 1), and the electronic inductive effect eventually makes the O6 atom in TS_{5-II}^C carry a greater negative charge than that in TS_{5-II}^T . Therefore, the hydrogen atom on the O2 atom is more inclined to migrate to the O6 atom with the larger electronegativity in TS_{5-II}^C than in TS_{5-II}^T . The conversion from IM_5^T to II^T is calculated to be endothermic by 15.67 kcal mol⁻¹ with a barrier of 18.18 kcal mol⁻¹ as for the separate reactants. From II^T , the hydrogen on the O2 atom is directly transferred to the C8 atom via transition state TS_{II-III}^T . However, the energy of TS_{II-III}^T is up to 34.73 kcal mol⁻¹, less stable than TS_{II-III}^C by 19.70 kcal mol⁻¹, indicating that this process is kinetically unfavorable. The forward IRC calculation confirms that TS_{II-III}^T connects III^T , which lies 11.84 kcal mol⁻¹ below the reaction entrance.

Because of the considerable distances between the C4 and C10 atoms, III^C and III^T are not the best precursors for the following reactions. The conformational torsion around the

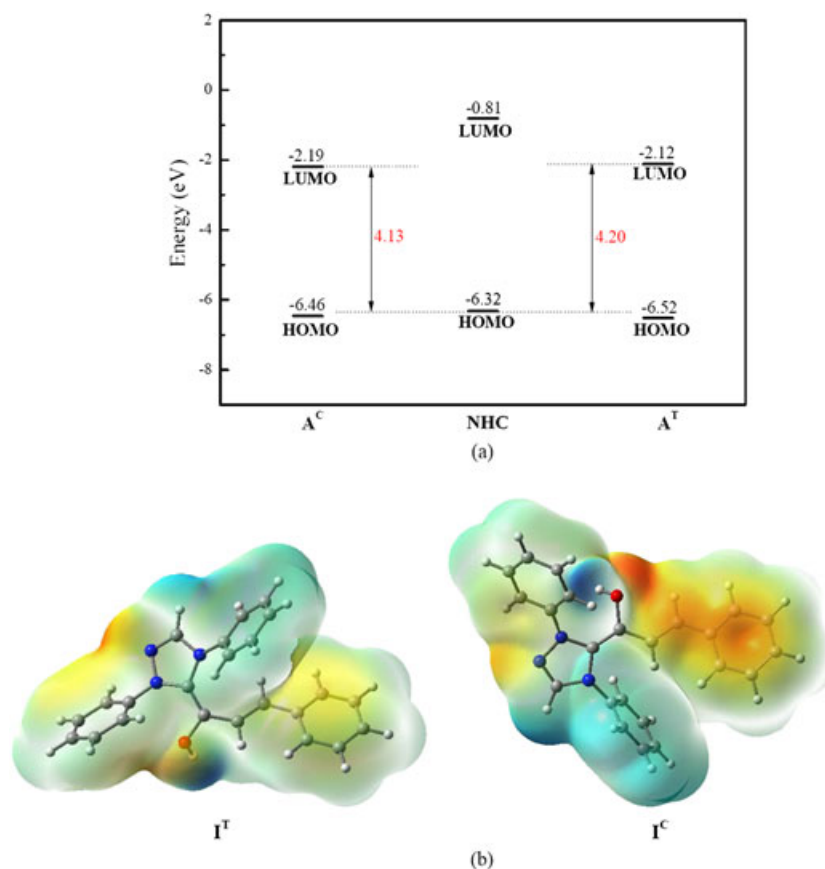


Fig. 5. (a) Energies of the HOMOs and LUMOs for NHC and A (A^C and A^T). (b) The electrostatic potentials of I^T and I^C mapped on the molecular isodensity surface ($P=0.02$ a.u.). Color scheme ranges for red (-0.06 a.u.) via green to blue (0.06 a.u.).

TABLE 1. Calculated partial charges from NPA analyses

	C5	O6	C7	C8	C9
TS_{5-II}^C	-0.291	-0.755	0.426	-0.391	-0.197
TS_{5-II}^T	-0.274	-0.748	0.427	-0.374	-0.212

C5-C9 bond must be undergone for the generation of more suitable precursors IM_6^C/IM_6^T (Fig. 4). Although the transition state structures for the conversion from III^C/III^T to IM_6^C/IM_6^T were not located in this work, the corresponding barriers are expected to be small since the processes involve a torsional deformation rather than bond breaking/formation. From IM_6^C/IM_6^T , the desired intramolecular addition reactions proceed to form the second C-C bond via TS_{6-IV}^C and TS_{6-IV}^T , which are only 1.22 and 5.21 kcal mol⁻¹ higher than the isolate reactants (see Fig. 4). The resulting adducts are IV^C and IV^T , which are accompanied by the energy releases of 10.84 and 3.46 kcal mol⁻¹, respectively. Further, along the reaction coordinate we located two transition states for the generation of the final product **C** and the release of NHC, TS_{IV-C}^C , and TS_{IV-C}^T , where the O11 atom is nucleophilically attacking the C1 atom, and at the same time the catalyst NHC is leaving. The energies associated with TS_{IV-C}^C and TS_{IV-C}^T are -7.30 and -2.22 kcal mol⁻¹ as for the reaction entrance, and the formations of C_{NHC}^C and C_{NHC}^T are calculated to release 24.44 and 25.55 kcal mol⁻¹ heat. Hereto, a catalytic cycle is completed. In the reaction processes shown in Figure 4, the large energy difference between the *cis*

and *trans* structures was also observed. This can be understood from the electronic effects combining with the spatial conformations of the structures. As the C4 atom nucleophilically attacks the C10 atom to form the second C-C bond, more negative charge will be transferred to the O11 atom, and more positive charge will concentrate on the C1 and C3 atoms. As shown by TS_{6-IV}^C and TS_{6-IV}^T in Figure 4, the distances between the C1/C3 and O11 atoms in TS_{6-IV}^C and TS_{6-IV}^T are 2.938/2.731 and 3.576/4.131 Å, respectively. The shorter distances between positive and negative charges indicate a stronger electrostatic interaction, and thus lead to more stable structures. Therefore, the energies of the *cis* structures are lower than those of the *trans* structures.

To summarize the above discussion, the cascade annulation reactions between I^C/I^T and **B** involve four elementary steps. The conformational difference of I^C and I^T leads to two slightly different annulation reaction processes, and the reaction process involving I^C is more kinetically favorable, because of the stronger nucleophilic reactivity of I^C than I^T . This is in good agreement with the reaction tendency of the first stage of this catalytic reaction. In the second stage of this catalytic reaction containing I^C , the hydrogen transfer step needs to cost the largest energy of 15.03 kcal mol⁻¹, which is much less than the energy consumption of 23.14 kcal mol⁻¹ for the DBU-assisted C1 proton departure in the first stage of this catalytic reaction. This fact indicates that the rate-determining step of the total reaction is the DBU-assisted C1 proton departure process.

Furthermore, to understand why the expected cyclopentene-containing products were not detected in the experiment, we also studied the aldol cyclization process of intermediate **III^C**. It was found that the transition state (see Supporting Fig. S2) for the aldol cyclization of **III^C** lies 7.01 kcal mol⁻¹ above the reaction entrance, which is 5.79 kcal mol⁻¹ higher than TS_{6-IV}^C for the intramolecular addition causing the C4-C10 bond formation. The calculated results indicate that, from **III^C**, the intramolecular addition reaction occurs more easily than the aldol cyclization. This rationalizes the experimental observation.

CONCLUSION

In this study we carried out a detailed theoretical study for the annulation reaction of cinnamaldehyde and benzodi(enone) catalyzed by NHC in the presence of DBU. By performing DFT calculations, we show clearly the micromechanism details and provide a reasonable explanation for the experimental observation.

In the present work, the annulation reaction of cinnamaldehyde and benzodi(enone) catalyzed by NHC in the presence of DBU falls into two stages: the formation of homoenolate intermediate and the annulation of homoenolate intermediate with benzodi(enone). In the first stage of this catalytic reaction, three paths are characterized for the generation of homoenolate intermediate, in which path III proposed by us involving the DBU-assisted 1,2-proton transfer with a stepwise mechanism is found to be kinetically more favorable, and the DBU-assisted C1 proton departure is the rate-determining step of the total reaction. In the second stage of this catalytic reaction, the cascade annulation of homoenolate intermediate with benzodi(enone) involves four elementary steps, and the conformational difference of **I^C** and **I^T** leads to two slightly different annulation reaction processes. In the whole reaction, the process involving *cis*-cinnamaldehyde is kinetically more feasible. The apparent superiority of the *cis*-conformation in energy can be clearly understood through the FMO analysis and the electronic inductive effect. Furthermore, the higher energy cost for the aldol cyclization of intermediate **III^C** than the intramolecular addition causing the C4-C10 bond formation provides a reasonable explanation for the experimental observation that the expected cyclopentene-containing products were not detected in the experiment.

The calculated results are expected to offer valuable information for further design and development of NHC-mediated reactions.

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