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Theoretical Studies on the Activation Mechanism Involving Bifunctional Tertiary Amine–Thioureas and Isatylidene Malononitriles

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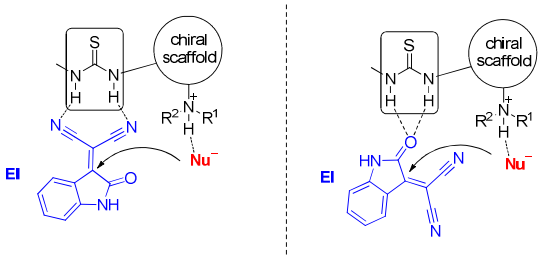
Computational studies have been performed to elucidate the activation mechanism of the Michael addition reactions containing bifunctional tertiary amine–thioureas and isatylidene malononitriles by density functional theory (DFT) calculations with the B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) level of theory. Results showed a difference of 6.47 kcal/mol between **M1-O** and **M1-N**, which suggest that it is the carbonyl group, instead of the malononitrile moiety of isatylidene malononitriles, that plays a dominating role in the activation of the electrophile by the catalysts. The predicted mechanism also successfully explains experimentally observed enantioselectivity.

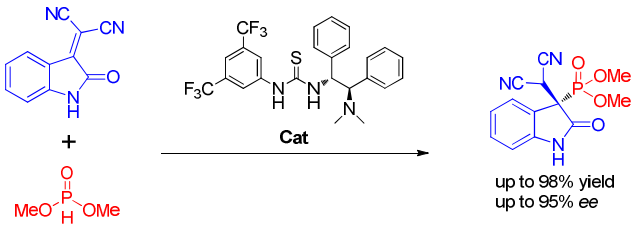
Introduction

Asymmetric organocatalysis has attracted increasing interests throughout the world since 2000.[1] Over one decade, the design of new catalysts, the synthetic applications and the study of the catalytic mechanisms have been evolving interactively. Non-covalent asymmetric organocatalysis, in which enantiomerically pure small organic molecules with hydrogen bonding are primarily designed as chiral catalysts for asymmetric transformations, has became as a powerful catalytic method for current organic synthesis.[2] Decades of experimental researches and computational studies, actually inspired by the findings on enzymatic activation, have revealed that hydrogen bonding is a key contributor for recognition and activation of specific substrates.[3] Subsequently, the discovery of bifunctional acid-base catalysts have greatly enriched the methods of asymmetric organocatalysis. In particular, the bifunctional tertiary amine-thiourea system, first designed by Takemoto group,[4] plays a unique role due to its widespread application in the field of catalytic asymmetric synthesis.[5] For common acceptable catalytic model, the effect of hydrogen bonding of the thiourea backbone to an electrophile leads to decrease the energy of the electrophile's lowest unoccupied molecular orbital (LUMO), activating it toward nucleophilic attack. Simultaneously, tertiary amine motif functions as a deprotonation agent to generate the required nucleophile.

Recently, an interesting Michael acceptor, named isatylidene malononitrile, is used to construct potential bio-active molecules under the catalysis of the bifunctional thioureas.[6] According to the multifunctional structure of the electrophile, two reaction mechanisms were mainly proposed.[6a,b] In 2012, Wang and coworkers first proposed that the thiourea moiety of bifunctional thioureas forms weak hydrogen bonds with the dicyano groups of the electrophile, which results in a double hydrogen-bonding aggregate (left, Scheme 1).[6a] In contrast, Yan et al. supported the mechanism involving the hydrogen bonds between the carbonyl of the isatylidene malononitrile and the catalyst (right, Scheme 1).[6b] As one of our ongoing research interests, we are interested in designing catalytic asymmetric reactions by bifunctional thioureas and isatylidene malononitriles.[6c–e] More importantly, as far as we know, the multifunctionality of the reactants effect on these reactions is less known theoretically until now. Thus, we regard this research field as very important. The present work makes such an effort to investigate the effects of the electrophile (isatylidene malononitrile) on the asymmetric Michael additions through our theoretical calculations. Herein, we report the reaction mechanism on an asymmetric conjugate addition of dimethyl phosphites to isatylidene malononitriles catalyzed by bifunctional tertiary amine-thiourea (Scheme 2)[6c] by density functional theory (DFT) calculations using Gaussian 09 suite of program with the B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) level of theory,[7,8] hopefully providing further insights into the understanding of hydrogen-bond-mediated catalysis. This level of theory was demonstrated to be appropriate for studying the hydrogen-bond-mediated catalytic reactions.[3a–i] Additional computational details are available in the Electronic Supplementary Information.



Scheme 1 Two proposed transition states by Wang et al. (left) and Yan et al. (right).



Scheme 2. Asymmetric conjugate addition of dimethyl phosphites to isatylidene malononitriles catalyzed by bifunctional tertiary amine-thiourea.

Results and discussion

Similar to the previous theoretical studies reported by Pápai et al. and Wang et al.,[3a,h] the bifunctional thiourea, **Cat**, first easily coordinates with the nucleophile (dimethyl phosphite), **Nu**, and subsequent protonation occurs from **Nu** to **Cat**, enhancing the nucleophilicity of **Nu**. Transition state **Cat-TS-CatH** connects the reactant **Cat-Nu** and the intermediate **CatH-Nu** with a negligible activation barrier of 1.13 kcal/mol (Fig. 1). Therefore, not surprisingly, such a protonation process can easily take place. The formation of N–H bond between **Nu** and **Cat** leading to the intermediate **CatH-Nu** releases relatively smaller amount of the energy (1.30 kcal/mol).

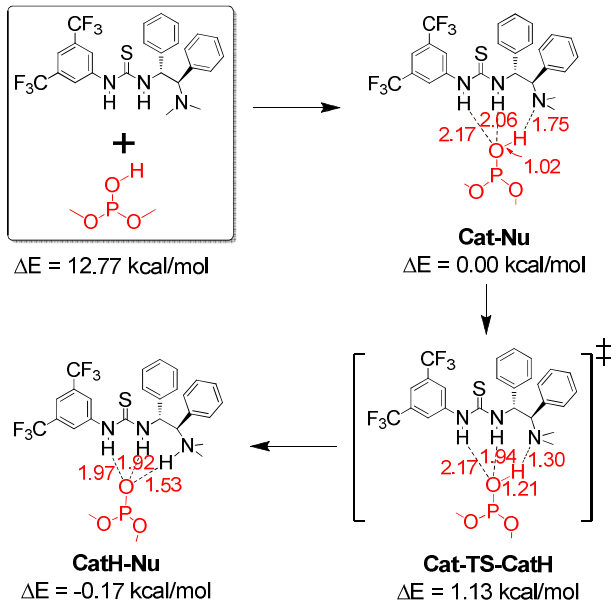


Fig. 1 Formation of **Cat-Nu** complexes and the process of **Cat** protonation.

With respect to the proposed mechanism by Takemoto et al.,[9] the electrophile (isatylidene malononitrile), **EI**, was activated initially by the N–H groups of thiourea, meanwhile **Nu** was activated by the N–H of protonated catalyst. As expected, we have located two possible intermediates with multiple hydrogen-bonding interactions between **EI** and **Nu** (Fig. 2), **M1-O** and **M1-N**, concerning different activation model of **EI**. In **M1-O**, **EI** was activated by the catalyst via a hydrogen bond (2.16 Å) between one N–H group of the thiourea and the carbonyl of **EI**. Simultaneously, it is notable that the N–H of **EI** also forms a hydrogen bond (2.13 Å) with a fluorine atom of one trifluoromethyl of **Cat**. Such a ternary complex **M1-O** ensures that **Nu** could conceivably only attack **EI** at the *Re*-face, leading to the corresponding *R*-configured product. In **M1-N**, it can be activated through hydrogen-bonding interactions between one cyano group of **EI** and one N–H group of **Cat** (Fig. 2). Obviously, **M1-O** is more stable than **M1-N** by 6.47 kcal/mol, indicating the activation starting from **M1-O** was more favorable. By the way, our attempts to locate the intermediate in which two cyano groups of **EI** forming hydrogen bonds with **Cat** as Wang et al.[6a] proposed (left in Scheme 1) failed. As shown in the Supplementary Information, it may be due to the overlong distance (4.31 Å) between two rigid cyano groups of **EI** as well as the shorter distance (2.20 Å) of two hydrogen atoms of thiourea group of **Cat**.

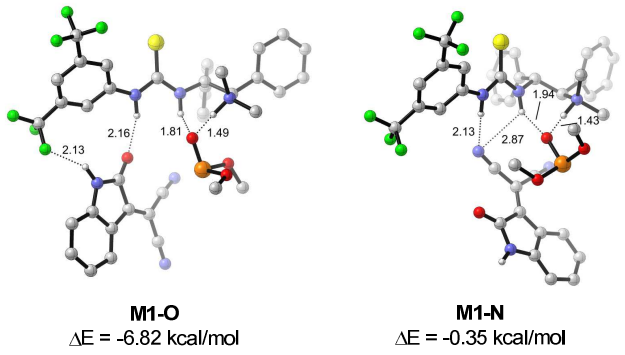


Fig. 2 Optimized structures and selected geometric parameters of the intermediates, **M1-O** and **M1-N**.

After **M1-O**, once the dual activation is accomplished, the P–C bond formation between **EI** and **Nu** takes place via transition state $\mathbf{TS_{P\text{-}C}}$ with a relatively low energy barrier of 2.92 kcal/mol. Seen from Fig. 3, transition state $\mathbf{TS_{P\text{-}C}}$ is stabilized by the hydrogen-bonding interactions between **Cat** and the two substrates (**EI** and **Nu**). Surely, the charge transfer occurring from the anionic **Nu** to **EI**, charge delocalization, the hydrogen-bonding interactions between **Cat** and **EI** are enhanced in $\mathbf{TS_{P\text{-}C}}$, meanwhile the interaction between **Cat** and **Nu** is weakened.

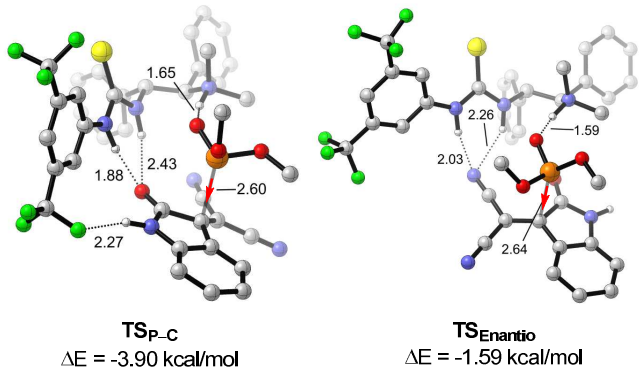


Fig. 3 Optimized structures and selected geometric parameters of transition states, which afford the *R*-configured product, $\mathbf{TS_{P\text{-}C}}$, and *S*-configured product, $\mathbf{TS_{Enantio}}$, respectively.

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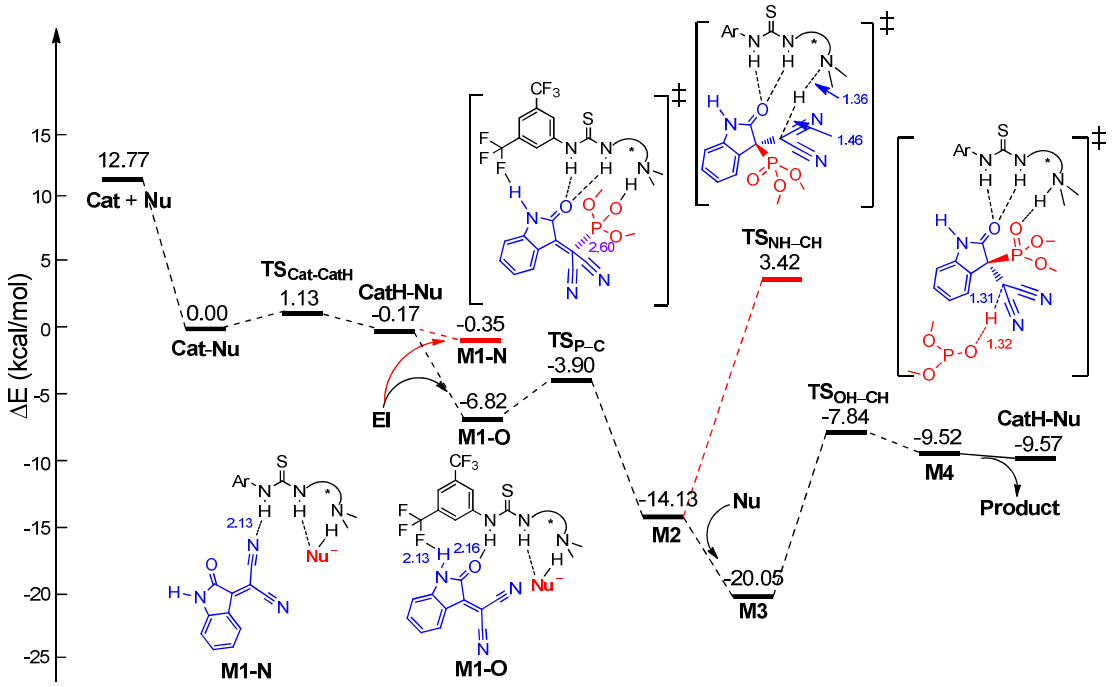

Figure 4. Energy profiles of the reaction pathway corresponding to the formation of the *R*-configured product.

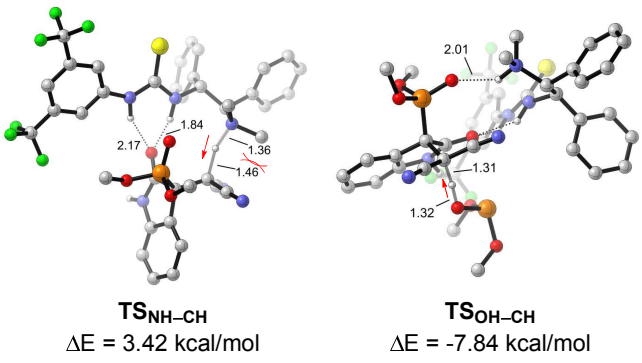

Fig. 5 Optimized structures and selected geometric parameters of transition states, $\mathbf{TS_{NH\text{-}CH}}$ and $\mathbf{TS_{OH\text{-}CH}}$, which could afford the final product.

To further validate such an activation mechanism, we also conducted DFT calculations to evidence the origin of the enantioselectivity which is certainly controlled in the P–C bond formation step. The transition state $\mathbf{TS_{Enantio}}$ (Fig. 3) which could lead to the opposite configuration product, is found to be 2.31 kcal/mol less stable than $\mathbf{TS_{P\text{-}C}}$. The energy difference is in good agreement with the experimental result (90% ee).[6c] The main difference between these two transition states is the activation model of **EI** catalyzed by **Cat**. In $\mathbf{TS_{P\text{-}C}}$, strong hydrogen-bonding interactions between the carbonyl and N–H of **EI** and **Cat** are formed, while in $\mathbf{TS_{Enantio}}$, only one cyano group of **EI** could be connected to **Cat** through weaker hydrogen bonds.

The last stage of the catalytic cycle is the formation of the final product and the recovery of **Cat**. After the formation of P–C bond via $\mathbf{TS_{P\text{-}C}}$ (Fig. 4), intermediate **M2** is generated and subsequently captures a proton from the second **Nu** through $\mathbf{TS_{OH\text{-}CH}}$. Then the final product dissociates from **Cat**. With respect to the previous studies by Wang et al.,[3h] we first locate the transition state $\mathbf{TS_{NH\text{-}CH}}$ (Fig. 5) in which a proton transfers from the amine group of **Cat** to **EI**. However, the energy barrier of such a process is larger with the energy of 17.55 kcal/mol (**M2**→$\mathbf{TS_{NH\text{-}CH}}$). The high energy barrier may contribute to the steric repulsion between **Cat** and the dicyano groups of the adduct which is generated through $\mathbf{TS_{P\text{-}C}}$, destabilizing $\mathbf{TS_{NH\text{-}CH}}$. On the other hand, transition state $\mathbf{TS_{OH\text{-}CH}}$ connects intermediate **M3** and **M4** with a relatively lower barrier of 12.21 kcal/mol than that (17.55 kcal/mol) of the corresponding path via $\mathbf{TS_{NH\text{-}CH}}$ (Figure 4). In $\mathbf{TS_{OH\text{-}CH}}$, an extra **Nu**, which serves as a proton donor, is included, differing from proton donor in $\mathbf{TS_{NH\text{-}CH}}$. Thus, the dicyano groups of the adduct in $\mathbf{TS_{OH\text{-}CH}}$ are positioned away from the amine part of **Cat**.

In Fig. 4, the proton transferring from the second **Nu** to **EI** is the rate-determining step (**M3**→$\mathbf{TS_{OH\text{-}CH}}$) with activation barrier of 12.21 kcal/mol, which represents a moderate barrier height. The intermediate **M4**, a ternary complex, is thus generated via $\mathbf{TS_{OH\text{-}CH}}$

by releasing a small amount of energy of 1.68 kcal/mol. Finally, the product **Prod** is extruded from **M4** to regenerate the **Nu**-coordinated catalyst, **CatH-Nu**.

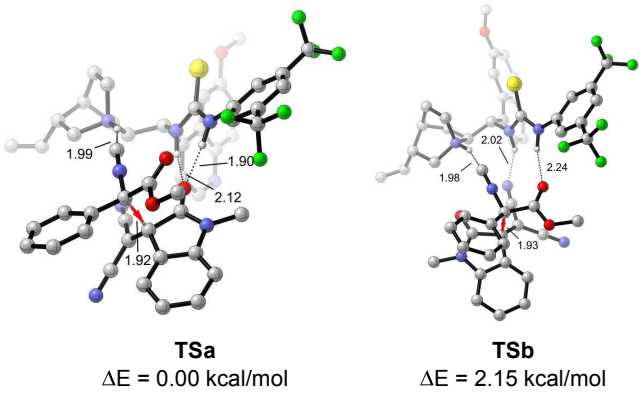

Fig. 6 Optimized structures and selected geometric parameters of transition states, **TSa** and **TSb**, which could afford a pair of enantiomers.

In addition, theoretical calculations on the Michael addition reactions between isocyanoacetate and isatylidene malononitrile catalyzed by a tertiary amine–thiourea derived from quinine are also carefully conducted.[6b] As shown in Fig. 6, transition state **TSa**, which could lead to the main product experimentally generated, is 2.15 kcal/mol more stable than transition state **TSb**, which corresponds to the reverse-configured product. The *N*-substituted isatylidene malononitrile in **TSa** is activated through hydrogen-bonding interactions (2.12 Å and 1.90 Å) with the catalyst. That is to say, for the electrophile, *N*-substituted isatylidene malononitrile, it is also the carbonyl group, rather than the malonitrile group, that plays a dominant role in the activation. In contrast, in **TSb**, there is only one hydrogen bond (2.02 Å) formed between one cyano group of the electrophile and one N–H of the thiourea catalyst.

Conclusions

In conclusion, computational investigations have been used to explore the detailed mechanism of Michael additions involving bifunctional tertiary amine-thioureas and isatylidene malononitriles. Our calculations clearly exhibit the activation model of isatylidene malononitriles catalyzed by bifunctional tertiary amine-thioureas. Due to the relative stabilization of intermediates **M1-O** (-6.82 kcal/mol) and **M1-N** (-0.35 kcal/mol), multiple hydrogen-bonding interactions are of critical. The carbonyl group could form a more stable hydrogen-bonding aggregate with the bifunctional thioureas than the dicyano groups. Similar results are also obtained in the Michael addition of isocyanoacetate to isatylidene malononitrile. Besides, these mechanistic studies are of fundamental importance in light of the design of new organocatalytic synthesis of potential bio-active molecules derived from isatylidene malononitriles. Further investigations, which involve the use of bifunctional thioureas in asymmetric organocatalysis, are still ongoing in our labs and will be reported in near future.

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† Electronic Supplementary Information (ESI) available: Details of computational methods, complete ref 7, cartesian coordinates, and energies of all reported structures. See DOI: 10.1039/c000000x/

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