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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. Noncovalent asymmetric organocatalysis, in which enantioselectively pure small organic molecules with hydrogen bonding are primarily designed as chiral catalysts for asymmetric transformations, has become 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.7a–e 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).
Results and discussion

Similar to the previous theoretical studies reported by Pápai et al. and Wang et al., 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).

After M1-O, once the dual activation is accomplished, the P–C bond formation between EI and Nu takes place via transition state TS_{P-C} with a relatively low energy barrier of 2.92 kcal/mol. Seen from Fig. 3, transition state TS_{P-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 TS_{P-C}, meanwhile the interaction between Cat and Nu is weakened.
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 TS_{Enantio} (Fig. 3) which could lead to the opposite configuration product, is found to be 2.31 kcal/mol less stable than TS_{P-C}. The energy difference is in good agreement with the experimental result (90% ee).3c The main difference between these two transition states is the activation model of EI catalyzed by Cat. In TS_{P-C}, strong hydrogen-bonding interactions between the carbonyl and N–H of EI and Cat are formed, while in 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 TS_{P-C} (Fig. 4), intermediate M2 is generated and subsequently captures a proton from the second Nu through TS_{OH-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 TS_{NH-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 \rightarrow TS_{NH-CH}). The high energy barrier may contribute to the steric repulsion between Cat and the dicyano groups of the adduct which is generated through TS_{P-C}, destabilizing TS_{NH-CH}. On the other hand, transition state TS_{OH-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 TS_{NH-CH} (Figure 4). In TS_{OH-CH}, an extra Nu, which serves as a proton donor, is included, differing from proton donor in TS_{NH-CH}. Thus, the dicyano groups of the adduct in TS_{OH-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 \rightarrow TS_{OH-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 TS_{OH-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.

In addition, theoretical calculations on the Michael addition reactions between isocyanooacetate and isatylidene malononitrile catalyzed by a tertiary amine–thiourea derived from quinine are also carefully conducted. 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 malononitrile 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 isocyanooacetate to isatylidene malononitrile. Besides, these mechanistic studies are of fundamental importance in light of the design of new organocatalytic synthesis of potential bioactive 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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Notes and references

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