

Computational Mechanistic Studies on Organocatalytic Addition Reactions

Theses of PhD dissertation

Tamás Földes

Supervisor:

Imre Pápai, D.Sc.

Head of Research Group

Theoretical Chemistry Research Group

Research Centre for Natural Sciences

Hungarian Academy of Sciences

Eötvös Loránd University

Hevesy György PhD School of Chemistry

Head of School: Attila Császár, D.Sc.

Theoretical and Physical Chemistry,

Structural Chemistry PhD Program

Head of Program: Péter Surján, D.Sc.

1. Introduction

Standalone computational investigations or studies involving both experimental and complementary computational explorations have contributed significantly to the advancement of chemical catalysis. Quantum mechanical calculations, particularly density functional theory (DFT) based approaches became widely applied, because they are generally assumed to provide reasonably accurate structural and energetic data at the molecular level even for relatively large chemical systems [1].

During my PhD work, I have been involved in computational mechanistic studies of organocatalytic reactions. Organocatalysis rose less than two decades ago as a promising and intriguing way of asymmetric catalysis; and its ease, low-cost, and safety allowed the rapid expansion of the field in synthetic chemistry [2]. This particular class of catalysis employs small molecules to activate organic substrates in a manner that is reminiscent of enzyme catalysis [3]. Similarly, these catalysts generally function through analogous activation mechanisms; these range from hydrogen-bonding interactions through to the formation of covalently bound intermediates [4]. As a consequence, it has not only provided interesting and powerful opportunities to synthetic chemists, but has also attracted the attention of computational experts. This is due to the immense advantage of deep mechanistic understanding in the design of new catalysts.

Our computational arsenal, alongside the experiments carried out by our collaborators, made us capable to gain insight into the mechanism of three organocatalysts that operate *via* distinct activation patterns; however, these works are connected by a few essential aspects. In all three cases, studies of the key intermediates and transition states helped us and our collaborators to interpret the experimental observations and exploit the catalytic systems. This was provided by the application of state-of-the-art theoretical approaches for a number of addition reactions.

2. Computational Methodology

We intended to acquire structural and thermochemical data (1) by reliable and affordable computational methods applied (2) on relevant molecular structures, followed by (3) careful analysis and critical quality assessment. In this regard we employed a powerful combination of conformational analyses and DFT computations.

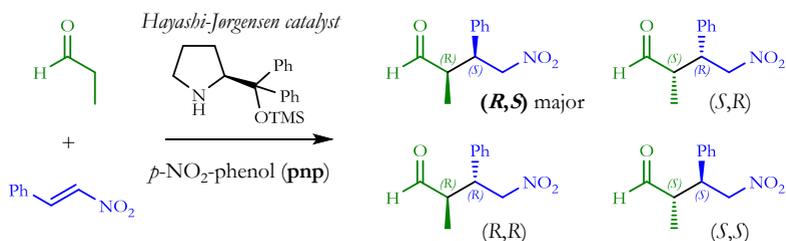
The complex Born-Oppenheimer potential energy surface (PES) of the molecular models (both intermediates and transition states (TS)) in the presented studies was explored systematically or via an automated molecular conformational analysis based on Monte Carlo sampling using a slightly modified version of the OPLS_2005 force field. The modification concerns the partial atomic charges used to estimate the energy contribution of Coulomb interactions. These parameters were obtained from preliminary DFT calculations as electrostatic potential (ESP) derived atomic charges. For each case, several (at least a dozen), structurally distinct conformers were selected for geometry optimizations, which were carried out *via* DFT calculations.

We employed hybrid density functional methods (ω B97X-D [5], M06-2X [6]) and located key stationary points on the PES *via* full geometry optimizations (with the triple- ζ basis set 6-311G(d,p)). For each located structure, we performed vibrational normal-mode analysis to verify the nature of the obtained stationary points (energy minimum or transition state) and also to estimate the thermal and entropic contributions for $T = 298.15$ K and $c = 1$ mol/dm³ conditions. These quantities were estimated within the typically used ideal gas rigid rotor-harmonic-oscillator approximations [7]. Electronic energies were calculated on the basis set 6-311++G(3df,3pd). Solvent effects were taken into account with the SMD (IEF-PCM) continuum solvation model [8].

3. Results and Discussion

3.1 Stereocontrol in the Hayashi-Jørgensen Catalyst Mediated Michael Addition of Propanal to β -Nitrostyrene

In this study [9] we carried out quantum chemical computations related to the conjugate addition reaction between propanal and nitrostyrene, mediated by the Hayashi-Jørgensen catalyst (Scheme 1). Our investigation addressed the origin of stereoselectivity, which was previously interpreted by two conflicting models, namely the *steric shielding model* and the *Curtin-Hammett scenario*. We focused on the key elementary steps of the reaction (C-C bonding and protonation) and combined our results to a comprehensive mechanistic model. In addition, we assessed the performance of our approach in order to increase the reliability of our conclusions. The main conclusions of our computational analysis are:



Scheme 1. The product isomers formed in the reaction between propanal and nitrostyrene.

- I./1. We identified the most favored TSs identified along the four different stereoisomeric C-C bond formation pathways and we demonstrated that they are consistent with the common *steric shielding model*, as the addition preferentially occurs on the unhindered face of the most favored *E*-enamine intermediate.
- I./2. We showed that the commonly applied acid co-catalyst **pnp** stabilizes the TSs of both C-C bond formation step and interconversion of downstream intermediates *via* hydrogen-bonding interactions that lower the related barriers.

I./3. Considering the obtained relative Gibbs free energies of the C-C bonding and protonation transition states (Figure 1), fast equilibration of the stereoisomeric cyclic intermediates is inconceivable, which rules out the applicability of the *Curtin-Hammett scenario* in this reaction; however, in agreement with experimental observations, our DFT computations suggest the protonation still to be rate-determining. Based on this finding, in combination with I./1., we suggest a new stereoselectivity model. In this model, the reaction rate is dictated by the protonation step, while the stereoselectivity is governed by the C-C bond formation transition states.

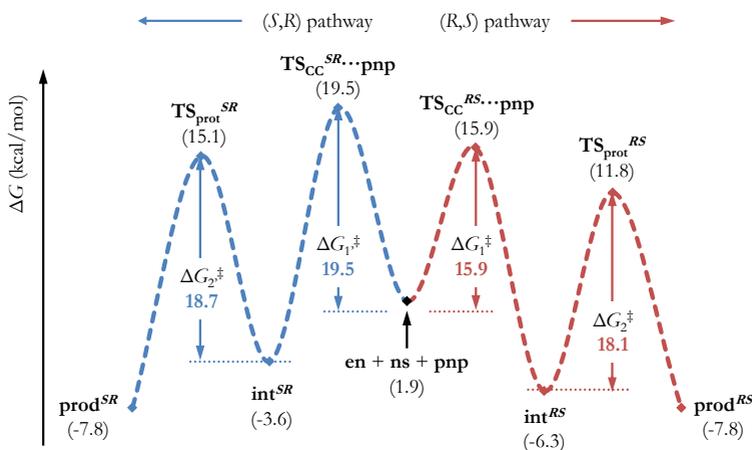


Figure 1. Free energy profile computed for the (R,S) and (S,R) pathways of the scrutinized Michael reaction in the presence of **pnp**.

I./4. Kinetic simulations, based on the computationally found two-step model, suggested that enantiomeric ratio (*er*) varies in time due to the delicate balance between the reaction barriers. Accordingly, we designed experiments, and the time-dependence of *er* could be demonstrated by ESI-MS measurements for the back reaction. This is only consistent with the proposed two-step stereoselectivity model.

I./5. Quality assessment of our methodology, based on *ab initio* computations and review of previous computational studies, revealed the necessity of conformational analysis and an adequate set of quantum chemical tools to draw reliable conclusions. According to these tests, our DFT computations on the key TSs have a systematic error of about 2-3 kcal/mol, which does not distort the obtained qualitative model. Moreover, the conformational analyses allowed us to identify more stable (by 2-6 kcal/mol) TSs than that reported in previous studies.

3.2 Mannich Reaction of Aromatic and Aliphatic Imines in the Active Pocket of Folded Bifunctional Organocatalyst

In this combined experimental-computational study [10], we addressed the unusual reactivity of cooperative bifunctional catalyst towards aliphatic imines in Mannich addition reactions (Figure 2). Structures of the free catalyst and several binary complexes were explored as well. To assess our computational results we also investigated the reaction of *para*-substituted aromatic imines. Based on our results, the following conclusions were drawn:

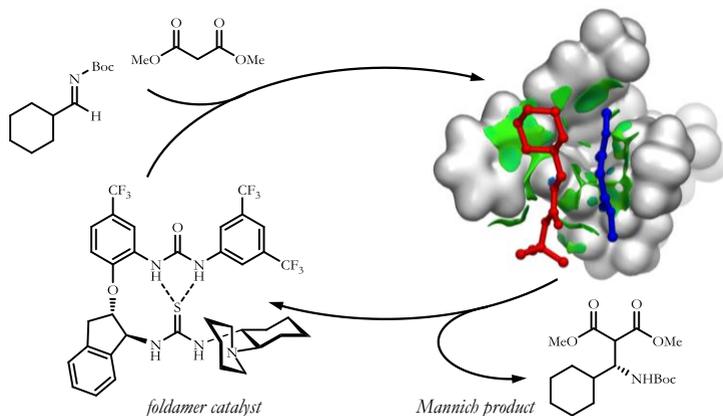


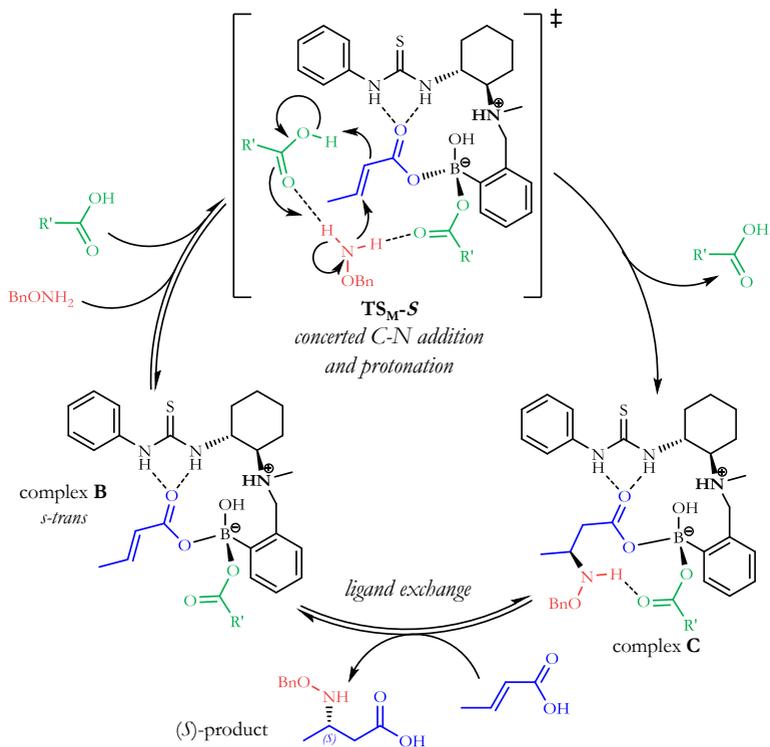
Figure 2. Mannich reaction of aliphatic imines mediated by foldamer catalyst.

- II./1. Both computations and X-ray structures suggest preference for the folded structure of the catalyst, which allows the formation of intramolecular cooperative hydrogen bonds.
- II./2. Quantum chemical computations revealed two viable pathways for the reactions, *route 1* and *route 2*, which differ in the substrate coordination to the catalysts hydrogen bond donor sites. Experimental and computed data point to a mechanism where the C-C bond formation is the rate-determining event.
- II./3. Our computational analyses suggest that, in addition to cooperativity effects, the foldamer catalyst can further facilitate the C-C bond formation *via* dispersion forces provided by the binding pocket created by the catalyst (Figure 2). These effects are practically negligible in the Takemoto catalyst, which might explain the superiority of foldamer catalyst over its predecessors in the reactions of aliphatic imines.

3.3 Mechanistic Insight into Asymmetric Aza-Michael Addition Catalysed by Multifunctional Thioureas

The multifunctional catalyst designed by Takemoto *et al.* was subject of thorough mechanistic investigation [11]. This catalyst, composed of a thiourea-based tertiary amine and arylboronic acid is able to effectively activate α,β -unsaturated carboxylic acids as electrophiles in aza-Michael reactions. Its conformationally more rigid structure allowed us to employ DFT computations, and in concert with experiments, to elucidate the reaction mechanism. The main conclusions of the computational work presented in this chapter can be summarized as follows:

- III./1. Computations indicated that in an energetically feasible conformation of the catalyst all catalytically relevant functional groups are simultaneously accessible for the substrates.



Scheme 2. Mechanism of the aza-Michael addition of α,β -unsaturated carboxylic acids (exemplified by crotonic acid).

III./2. In the most favored computed C-N bonding TS, the coordinating α,β -unsaturated carboxylic acid substrate is activated concurrently by the boronic acid and the thiourea unit, whereas the nucleophile is activated by a second coordinating acid. The lack of the latter interaction in the TS towards the minor product can account for the observed enantioselectivity of the reaction.

III./3. In agreement with the kinetic experiments, computations allude to the involvement of an extra carboxylic acid in the rate-determining step regardless, if the C-N bonding and the protonation occurs in concert or stepwise. Nevertheless, concerted asynchronous mechanism seems to be more plausible.

4. References

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4.1 Papers Forming the Basis of the Dissertation

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