Theoretical investigation of reaction mechanisms – from methodological development to applications

Summary of PhD dissertation

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1 Introduction

Numerical simulations and theoretical modelling of chemical reactions have become an emerging field of chemistry. The atomistic level insight provided by theoretical chemistry is an important asset in the development of new, more efficient chemical procedures. In particular the theoretical exploration of reaction mechanisms can assist the deeper understanding of synthetic reactions. My thesis summarizes our results in this field.

The first chapter of the thesis is an introduction to the theoretical framework of our studies. It summarizes the applied methods and theories; and contrasts them with alternative approaches. The second chapter focuses on the experimentally motivated research on organic and organometallic reactions. We have explored three complex reaction mechanisms in cooperation with the group of Zoltán Novák and thoroughly investigated the H₂ activation by three linked Frustrated Lewis-Pairs. Finally the last part of the thesis is based on our methodological developments in the fields of rate constant calculations and optimization of reaction coordinates.
2 Results

2.1 Palladium catalysed C–H activation [1]

We have studied the palladium catalysed C–H activation and coupling reaction of acetanilide and benzaldehyde in the presence of t-Butyl hydroperoxide (TBHP).

![Chemical structure](image)

**Figure 1.** oxidative coupling of acetanilide and benzaldehyde

The main conclusions from our mechanistic study are the followings:

- the rate determining step is the carbopalladation
- the catalytic effect of acids can be attributed to the stabilization of the active palladium mono-acetate complex by the protonation of the dissociated acetate ligands
- the C–C coupling proceeds through a bimetallic palladium complex
- the reductive elimination features a Pd(III)→Pd(I) process

Our mechanistic picture is in good agreement with recent experimental evidences concerning the rate determining step [7] and is supported by the presence of bimetallic complexes observed at similar reaction conditions [8].
2.2 Silver-mediated furan formation [2]

Lei and co-workers have reported a selective synthesis of substituted furans by the oxidative coupling of alkynes and β-keto esters [9]. We have investigated the mechanism of this interesting transformation. To this end we have examined the reaction between ethyl acetoacetate and phenylacetylene.

![Figure 2. Silver-mediated oxidative C-H/C-H functionalization](image)

The study provided us with the following important results:

- the C–C coupling reaction features the radical intermediate of ethyl acetoacetate and silver phenylacetylide
- the mechanism of the cyclisation reaction is ionic for terminal alkynes
- internal alkynes require higher activation for the C–C coupling reaction
- the cyclisation reaction of intermediates from internal alkynes proceeds through a radical pathway
- silver ions have double role in the reaction: radical generation and the catalysis of the ring formation
- the silver-furanyl organometallic intermediate decomposes before the acidic work-up of the reaction

Our mechanism is supported by vibrational spectroscopic observation of silver phenylacetylide and isotope labelling experiments. The presence of radical intermediates has been verified by experiments with scavengers.
2.3 Trifluoroethylation of indoles via C–H functionalization [3]

Our experimental partners have developed an efficient and selective synthetic procedure for C3 trifluoroethylation of indoles. The reaction required the presence of 2,6-di-tert-butylpyridine (DTBPy) in order to achieve maximum yield.

![Chemical reaction diagram]

**Figure 3.** Trifluoroethylation of indoles

Our mechanistic picture of the reaction can be summarized as follows:

- the C–C bond formation reaction is a direct electrophilic attack by the iodonium complex
- the role of the DTBPy is the deprotonation of the σ complex from the electrophilic attack
- in the absence of DTBPy, dimerization side reaction takes place
- bases with modest steric congestion undergo N-trifluoroethylation under the reaction conditions

Our scheme of competing N- and C-alkylations is able to predict the efficiency of a given substrate-base combination by computing activation barriers for these two elementary steps.
2.4 AIMD study of Frustrated Lewis-Pairs [4]

We have performed ab initio molecular dynamics in combination with free energy methods for the H₂ activation reaction of Frustrated Lewis-Pairs.

![Reactant state ensemble of the studied Frustrated Lewis-Pairs](image)

**Figure 4.** Reactant state ensemble of the studied Frustrated Lewis-Pairs

We have drawn the following conclusions from the simulations:

- we confirmed the cooperative, concerted heterolytic H₂ cleavage picture emerged from earlier static calculations

- structural parameters of the IRC configurations are also relevant in the finite temperature

- as a result of the asynchronicity of the activation, strong localization of the reaction enthalpy occurs on the proton in the product state

- the translational energy of H₂ plays important role in the activation
2.5 Divided Saddle Theory – new method for calculating rate constant [5]

We have derived a new theory and an efficient method to calculate rate constants from molecular dynamics simulations. Our method development can be summarized as follows:

- the rate constant is factorised to a dynamical $k_{SD}$ and a static quantity $\alpha_{RS}^{SD}$

- $\alpha_{RS}^{SD}$ can be calculated from the free energy profile along a suitable reaction coordinate

- $k_{SD}$ can be calculated from short dynamical trajectories initiated at the saddle region

- Bennett-Chandler-like methods [10] can be analytically derived from our method

- the method has been validated through numerical simulations

- in terms of the number of trajectories our method proved to be more efficient then the effective positive flux method

![Figure 5. Divided saddle chair – illustration for the divided states in our theory](image)
2.6 Committor map collective variable [6]

Rate constant calculations require the knowledge of a proper reaction coordinate. We have proposed a new approach in order to represent the committor, which is a widely accepted proper reaction coordinate [10]. Our study involved the following important points:

- we have proposed the property map for the representation of the committor
- the performance of this representation has been tested in numerical simulations
- a new algorithm has been proposed for selecting the configurations for the committor calculations from enhanced sampling simulations
- the convergence of the protocol has been studied for two different enhanced sampling methods

![Diagram](image)

**Figure 6.** Committor in grid-based and committor map representations for the conformational equilibrium of alanine dipetide
3 Papers Forming the Basis of the Dissertation


4 Literature References


