Closing report for
"Realistic simulations of catalytic chemical reactions in aquatic environment"
OTKA project K101115

The problems selected for this project address chemical reactivity issues by simulations employing suitable *state-of-the-art* quantum chemical methods. The systems investigated within the framework of the project can be divided into two groups:

A) reactions taking place in homogeneous phase, such as olefin oxidation processes (Wacker-type reaction) or cross coupling reactions;

B) reactions occuring in heterogeneous phase: redox processes at mineral-water interfaces.

During the project the original topics have been extended and now the results cover a wider range of systems as compared to the originally planned scope of the research. Especially part A offered more opportunities via collaboration of the Lendület group of Prof. Novák. On top of that, some methodological developments have been carried out within the project which are now planned to be employed in subsequent reactivity studies. During the project two PhD students have participated in the research. One PhD dissertation has been finished and successfully defended. In addition several other students participated in the project for shorter periods, and they learned the basic know-how of the quantum chemical calculations and applications. Due to unforeseen problems we have extended the original 3-year period of the project to 4 years. In the following the summary of these 4 years are given.

A) Theoretical studies of reactions in homogeneous phase [1-4]

1) Theoretical studies on coupling reactions [1-3]

In close collaborations with the Lendület group of Prof. Novák we identified the reaction mechanism of three different types of coupling reactions. Pd-catalyzed oxidative acylation of anilides under mild conditions in water has been developed recently where we could show that the rate detemining step is the C-H activation step and then an efficient dimer Pd-salt forms which then reacts with the acylation reactant and affords the desired products. Our reaction scheme therefore features the parallel mono and dimer routes where the latter is ca. 10 kcal/mol more favorable. [1]

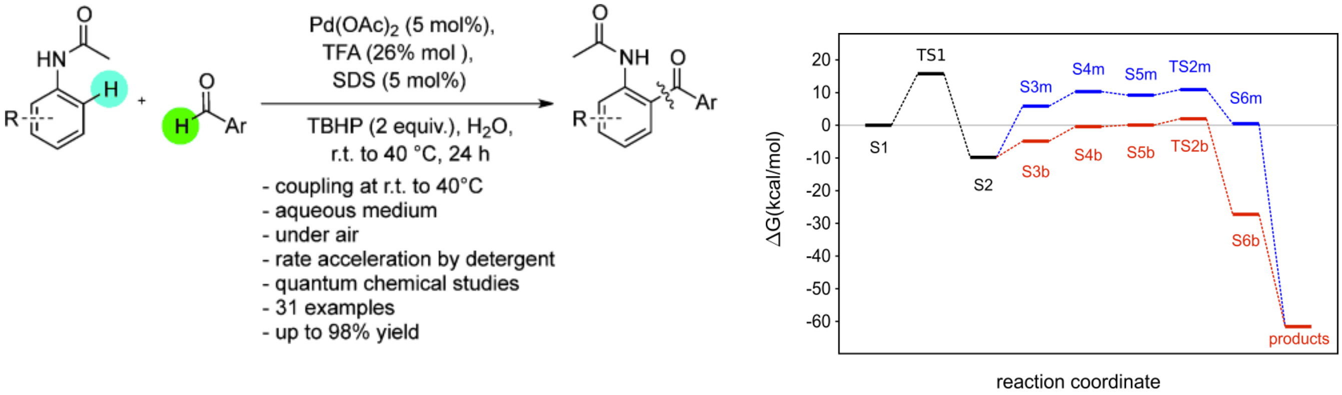

Figure 1. Oxidative Direct ortho-C-H Acylation of Anilides and the calculated free energy profiles

In another project [2] we have scrutinized a recently developed silver-mediated furan formation reaction by oxidative coupling. We have identified the elementary coupling and ring closure steps leading to the furan ring and described the reaction mechanism. We have found that the mechanism features a radical and a subsequent ionic route. The silver cation has a double role in the mechanism: it is the oxidant in the radical step and the catalyst for the ionic step. Our theoretical mechanistic insights have been verified by subsequent experiments. The publication has been labelled as *Hot paper* in Chem. Eur. J.

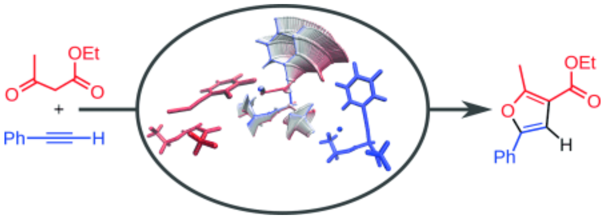

Figure 2. Ag-assisted C-C coupling as revealed by computation

In the next project we have identified the proper mechanism for metal free trifluoroethylation of indoles using 2,2,2-trifluoroethyl(mesityl)-iodonium triflate.[3] The C-C coupling step has proved to be the rate determining step. In this study we also had to explain the formation of undesirable side-product and the specific role of the selected base. This enabled us to formulate a more general strategy for the selection of the proper substrate-base combinations for designing new trifluoroethylated indole derivatives.

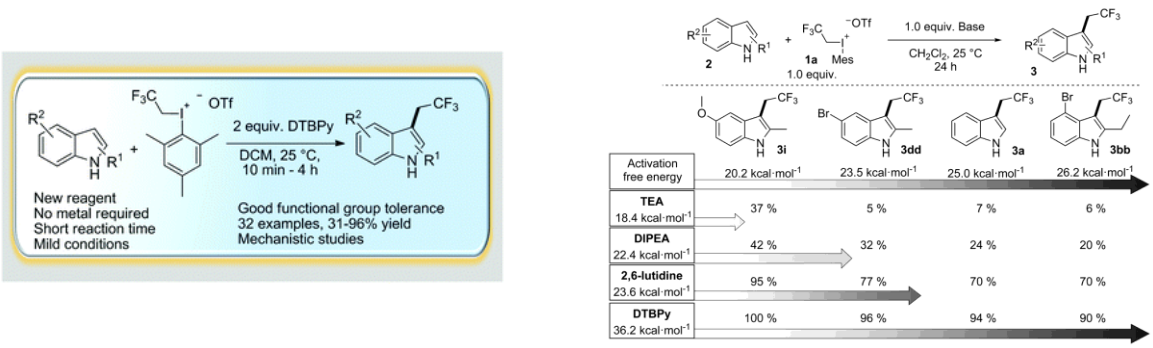

Figure 3. Efficiency of the trifluoroethylation of indoles for typical substrate-base combinations. Activation free energies: theory; conversions: experiment.

2) Simulations of the Wacker-reaction [4]

By request from the Chem. Soc. Rev. we had the opportunity to complete and summarize our earlier studies on the Wacker reaction.[4] In this review we exposed the experimental and theoretical challenges one might face in this field, and briefly reviewed the suitable free energy methods for simulating organometallic reactivity in water, where the solvent water has multiple roles in the reactions. A detailed summary of the mechanistic studies on the controversial steps of the Wacker reaction has been given and the rate determining step has been identified as the movement of a *cis-trans* chlorine anion movement in the Pd ion ligand sphere. In this review the efforts of two independent groups have been put together.

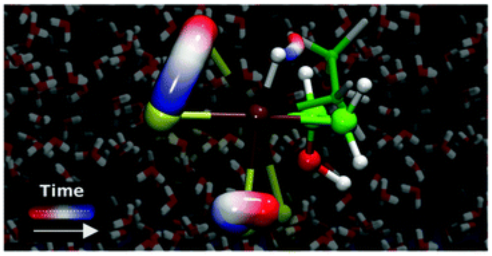

Figure 4. Atomic displacements during the rate determining step as seen by AIMD simulations.

3) Simulation of hydrolitic reaction [5]

For a request addressed to actual and ex-coworkers of Prof. Akira Miyamoto, I had the opportunity to conduct a project to the celebration of his retirement in a dedicated issue of the J. Comput. Chem. Jpn (peer-reviewed, but not ISI journal, no impact factor). [5] In this work I explored the process of SO_2 hydrolysis in water by ab initio molecular dynamics simulations. It has been obtained that the hydrated SO_2 is surrounded by the water molecules without any S-H hydrogen bond, restraining the sulfonate anion formation but allowing the bisulfite isomer formation. The simulations revealed that the hydrated SO_2 forms bisulfite anion and hydronium cation after overcoming a *ca.* 17 kcal/mol free energy barrier. Direct, one-step H_2SO_3 formation could not been observed, in sharp contrast with earlier cluster calculations. These findings indicate a step-wise H_2SO_3 formation in water. The presence of the sulfur lone pair represents an important constraint on the mechanism: the nucleophilic H_2O attack can occur only from certain angles as shown by the reactive trajectories.

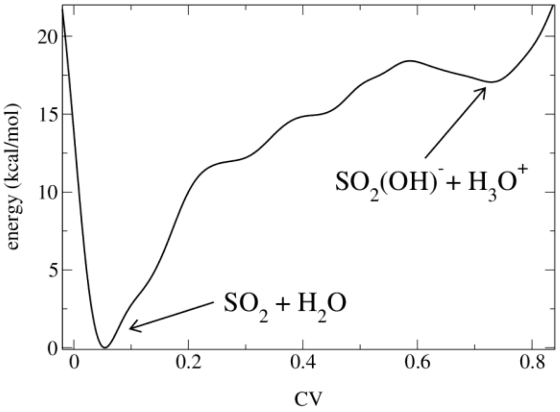

Figure 9. Free energy profile of the SO_2 hydrolysis.

B) Theoretical studies of reactions occurring in heterogeneous phase [6-8]

Oxidation of pyrite surface [6]

In order to understand the pyrite reactivity in aquatic environment an important ingredient is to describe the oxidation of the surface. Our calculations revealed the following plausible sequence of reaction steps for the incipient oxidation of pyrite surface: O_2 in molecular form adsorbs on iron sites in a side-on configuration before finding the most favorable S-vacancy sites. After dissociation, oxidation of sulfur sites are preferred although oxidation of iron sites are also favored thermodinamically. In particular the oxidation of S-adatom and saturation of S-vacancies are highly favorable at the initial stage of oxidation. This sequence is in agreement with experimental observations, it provides important insight into the incipient oxidation of pyrite and it is expected to assist the interpretation of XPS measurements.

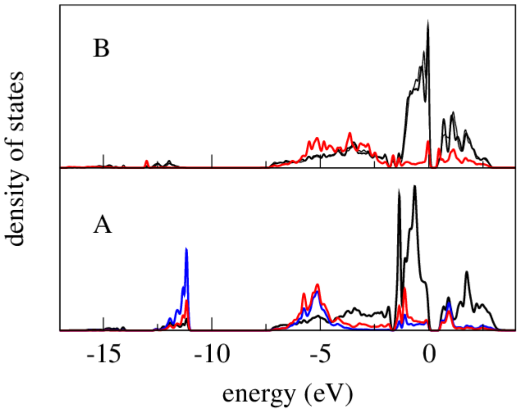

Figure 5. Atomic DOS curves obtained for an oxidized defective FeS_2 surface where the defective site is an S adatom (A) or a sulfur vacancy (B). The Fermi levels are set to zero in all cases. Color coding: black: Fe; blue: S; red: O.

Water-pyrite interface [7]

Continuing the expolarion of pyrite reactivity we have investigated the supercritical water-pyrite interface, because we wished to address reactivity issues under hydrothermal conditions, where water is in supercritical (SC) state. In particular these extrem conditions are relevant in the iron-sulfur world (ISW) theory, where prebiotic chemical reactions are postulated to occur at the mineral-water interface.

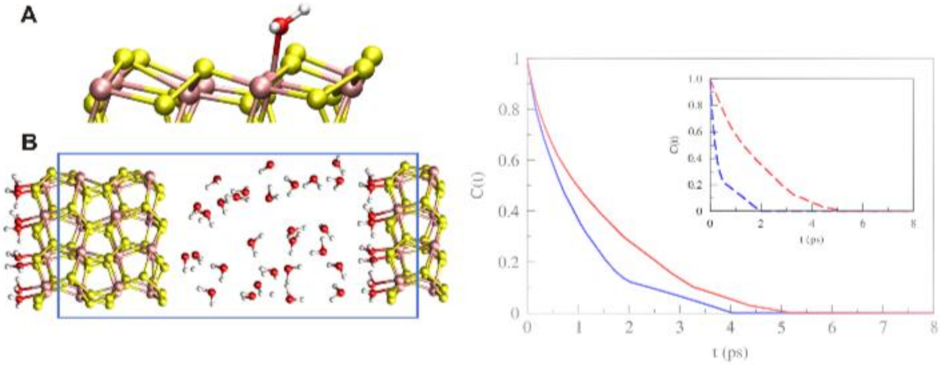

Figure 6. Interface models and continuous population autocorrelation functions of water binding on iron sites of FeS_2 (100) surface. Fur further details see Ref. [6].

Our results show that at SC conditions the water/pyrite interaction results in an almost completely dry surface even when defective (ie. more reactive) sites are present. These findings have important implications to the reactivity of pyrite. The SC conditions effectively eliminate the water adsorption layer from the surface and expose the topmost atoms and defective sites. Therefore both the iron and sulfur sites are available and a wide range of reactions is facilitated without prior water desorption. This picture is markedly different from that at ambient conditions where the surface is fully covered with adsorbed water molecules which is of relevance for the surface reactions of the ISW hypothesis.

Simulations of prebiotic NH_3 formation [8]

After having considered all the necessary prerequisite issues we have focused on the simulations of the reduction of NO_3^- and NO_2^- on FeS_2 surface under hydrothermal conditions as planned in the project. Overall the simulations suggest the following mechanistic picture: the $NO_3^- \rightarrow NH_3$ transformation can occur on a FeS_2 (100) surface in a stepwise single-atom transfer fashion. This process starts preferably on defect sites. The kinetic bottleneck of the full process is the reduction of NO^- bound to an iron surface site. Two quasi-equivalent paths operate simultaneously from the NHO species. I note that the reaction intermediates show striking analogy to those identified in the mechanism of nitrite reductase enzyme.

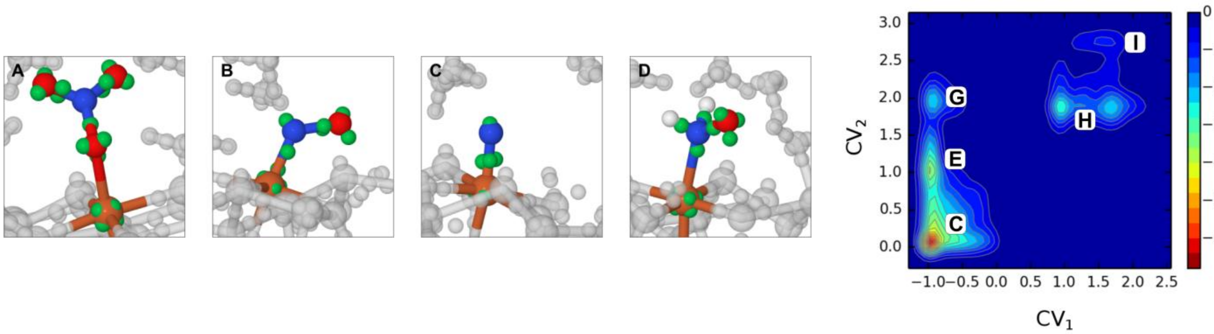

Figure 7. Left and middle: Centers (green balls) of maximally localized Wannier functions for different NO_xH_y intermediates adsorbed on pyrite surface.A: NO_3^-; B: NO^-; C: Fe(VI)-nitrido state; D: NH_2O^-. Wannier centers are very efficient in identifying the charge state of the adsorbed species and the iron site. Right: Free energy surface of the NO → NHO → NH_2O → NH_2 → NH_3 transformation occurring on a defective FeS_2 surface. The labels indicate the reaction stages according to the article. Further details and color code are given in Ref. [7].

Water participates in the processes as reactant and as an environment supplying the thermodynamic conditions which have a significant acceleration effect on the reactions. The role of pyrite in the process is twofold: it is a reactant and a support. It is a reactant by abstracting oxygen atoms stepwise. Its support role is to bind the N-containing species on the surface during the reactions, which allows for a simultaneous contact with water and the surface atoms for oxygen atom and proton transfers. The extreme conditions provide a particularly suitable interface arrangement [7] for this twofold role because the accessible surface sites are not covered by water thus providing room for both the adsorption and the reduction. Our model provides a plausible mechanistic picture of how NH_3 can form in hydrothermal vents which may have operated on the early Earth in the synthesis of prebiotic molecules. As ammonia is an essential prebiotic reactant, the present mechanistic picture provides further support for the role of iron sulfide minerals in the chemoautotrophic origin of life. The topic and the article has drawn the editors' attention and received *"ACS Aditors' Choice"* status and open access license.

C) Further related studies [9-11]

We have obtained results in a topic which has only partial overlap with the original plan.[9] We have studied a simple Frustrated Lewis acid-base pair (FLP) in toluene solvent using explicite solvent models (1 molecule FLP, 1000+ toluene molecules) employing classical force field modified with additional parameters obtained from quantum chemical calculations on related FLP models. The results point to low thermodynamical stability of associated states in dilute toluene solutions, but they also underline that encounter complexes can indeed be present in concentration typical of reactive intermediates. The monotonic decay of the calculated F(r) curve indicates a smooth transition between active and inactive associated forms emphasizing the elusive nature of encounter complexes.

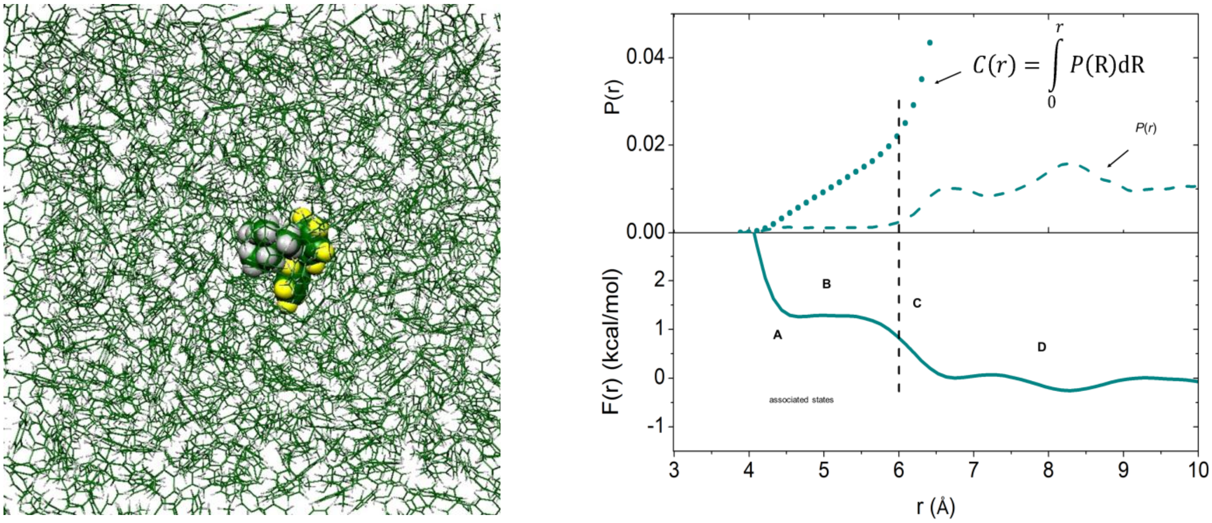

Figure 8. Left: FLP/solvent model. FLP: space filling model; wire-frame: toluene molecules. Right: Free energy curve F(r) and probability distribution P(r) computed from MD simulations for $(t\mathrm{Bu})_3\mathrm{P}/\mathrm{B}(\mathrm{C}_6\mathrm{F}_5)_3$ in toluene.

Methodological projects [10-11]

In the framework of the present OTKA activity we have investigated the possibility to use an inherently collective coordinate, the continuous symmetry measure (CSM) in describing reaction mechanisms and in following reaction courses. [10]

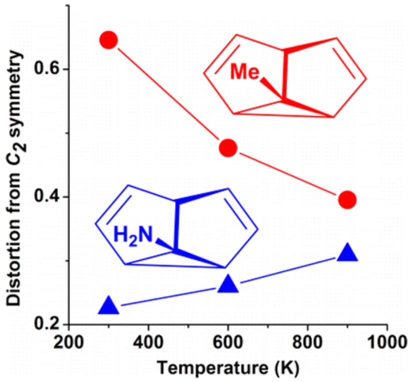

Figure 10. Effect of temperature and substitution on the symmetry properties of semibullvalenes.

It has tuned out various reactive transformations simulated by ab inito MD can be followed and analyzed efficiently by employing CSM. For example we have shown that in concerted reactions, ligands connected to the carbon frame have profound effect on the reaction course. In particular, our results show that lower temperatures tend to enhance the differences between the TS-stabilizing effect of the substituents.

We have developed a new method to calculate rate constants from simulations of reactive (rare) events. The formalism is based on the division of the saddle region of the free energy profile of the rare event into two adjacent segments called Saddle Domains. The method is built on sampling the dynamics within these regions: auxiliary rate constants are defined for the Saddle Domains and the absolute forward and backward rates are obtained by proper reweighting. We call our approach Divided Saddle Theory (DST). An important advantage of our approach is that it requires only standard computational techniques which are available in most molecular dynamics codes. The work has been published in the JCTC. [11]

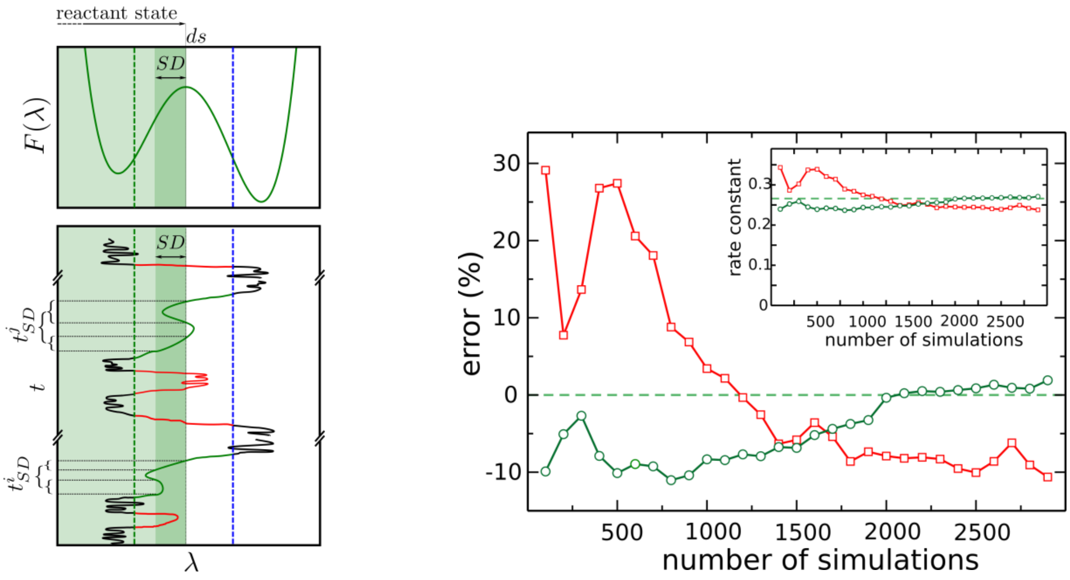

Figure 11. Left: Definition in the Divided Saddle Theory. Right: Convergence properties of the method based on DST compared with EPF method (another method based on the original Bennett-Chandler theory. For further details see Ref. [11].

D) Ongoing project

In the field of organometallic reactivity of water we are still working on an interesting project, where we address the ligand-sphere mobility and the consequent association-dissociation properties of several Pd(II) complexes which are highly relevant in homogeneous Pd(II)-catalysed processes. We have already successfully explored the free energy surfaces of the water-acetate exchanges on Pd(II) center and could identify the following mechanistic aspects: i) the step-wise water-substitutions are favorable processes in terms of free energy, which implies an equilibrium shifted toward the species containing coordinated water ligands; ii) the *trans* built-in is highly favored yielding monodentate acetate coordinations from the originally bidentate modes; iii) this is an efficiently preorganized form for the dimer formation; iv) formation of the *cis* configuration requires much higher free energy barrier and an ion-pair formation which needs higher free energy investment; v) the remarkable free energy difference between the *cis* and *trans* forms points to important constraints for the dimer formation and helps to define reliable routes for the association of the Pd(II) monomers. The dimer formation and dissociation is planned to explore in the next stage of the project. In particular, we plan to explore different configurations for the dimers and their formation and dissociation. The reaction mechanisms will be identified and characterized in terms of free energy changes and barriers as well as in terms of atomic-detailed description of the ligand sphere variations. The first part of the work is now being prepared for publication.

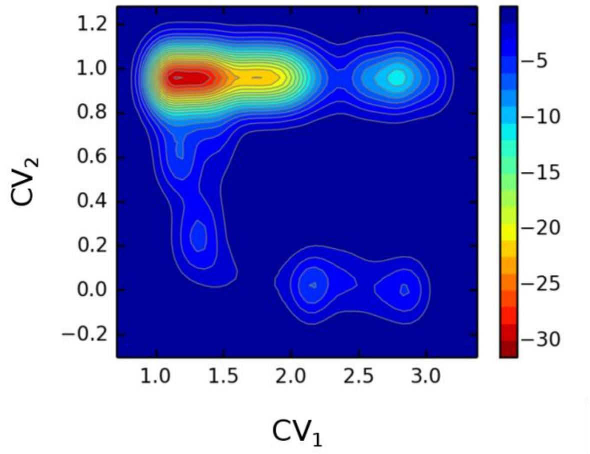

Figure 12. Free energy surface of the hydrolysis of $Pd(Ac)_2$, when a water molecule build in the first hydration spere, while an acetate anion leaves it.

Prior to and after the publications many of the results have been presented in conferences and workshops, such as ACS meeting, Central European Statistical Mechanics Mini-Meeting, KeMoMo-QSAR, CESTC, and in various universities. Participation of these meetings were also financed fully or partially by this OTKA activity.

The present OTKA activity has provided not only an excellent opportunity to perform the foregoing applications but it has also given ample opportunity to involve students into various stages of the applications. In fact, 8 students participated for shorter or longer period in this activity during the last four years. Dr. Daru has finished his PhD during this period. Mr. Bihari is still working on his PhD project. There were other 5 BSc and MSc students who performed calculations on a selected system realted to the projects. In addition a highly talented secondary-school student was also interested in such simulations and has been involved into one of the projects.

During the OTKA activity the computational needs became higher than originally planned therefore we applied and obtained significant CPU time from Switzerland (3.2 M CPUh) and from Spain (0.3 M CPUh). It is expected that we need to apply for foreign infrastructure for similar projects in the future.

In summary I believe that the present OTKA activity has been successful and it has resulted in a number of important publications. It has also defined new directions in our research and helped several students to appreciate the role and results of theory in interpreting experimentally observed reactivities. I wish to thank the OTKA for this Grant and for the opportunities this Grant has provided.

Publications of the project in the order of the report

[1] F. Szabó, J. Daru, D. Simkó, T. Zs. Nagy, A. Stirling , Z. Novák, *"Mild Palladium Catalyzed Oxidative Direct ortho-C-H Acylation of Anilides under Aqueous Conditions"* **Adv. Synth. Catal.**, 355 (2013) 685-691.

[2] J. Daru, Zs. Benda, A. Poti, Z. Novák, A. Stirling,*"Mechanistic study of silver-mediated furan formation by oxidative coupling"* **Chem. Eur. J.** 20 (2014) 15395-15400.

[3] G. L. Tolnai, A. Székely, Z. Makó, T. Gáti, J. Daru, T. Bihari, A. Stirling, Z. Novák, *"Efficient direct 2,2,2-trifluoroethylation of indoles via C–H functionalization"* **Chem. Comm.** 51 (2015) 4488-4491.

[4] A. Stirling, N. Nair, G. Ujaque, A. Lledos, *"Challenges in Modelling Homogeneous Catalysis: New Answers from Ab Initio Molecular Dynamics to the Controversy on the Wacker Process"* **Chem. Soc. Rev.**, 43 (2014) 4940-4952.

[5] A. Stirling, *"SO_2 hydrolysis: ab initio MD study of the formation of bisulfite ion"* **J. Comp. Chem, Japan**, 12 (2013) 38-42.

[6] T. Rozgonyi, A. Stirling, *"DFT Study of Oxidation States on Pyrite Surface Sites"* **J. Phys. Chem. C** 119, (2015) 7704-7710

[7] A. Stirling, T. Rozgonyi, M. Bernasconi and M. Krack, *"Pyrite in contact with supercritical water: The desolation of steam"* **PCCP**., 17, (2015) 17375-17379.

[8] A. Stirling, T. Rozgonyi, M. Krack and M. Bernasconi, *"Prebiotic NH_3 formation: insights from simulations"* **Inorg. Chem.** 55, (2016) 1934-1939.

[9] I. Bakó, A. Stirling, B. Szabolcs, I. Pápai, *"Association of frustrated phosphine-borane pairs in toluene: Molecular dynamics simulations"* **Dalton Trans.** 41 (2012) 9023-9025.

[10] I. Tuvi-Arad, T. Rozgonyi, A. Stirling, *"Effect of Temperature and Substitution on Cope Rearrangement: A Symmetry Perspective"* **J. Phys. Chem A**, 117 (2013) 12726-12733.

[11] J. Daru, A. Stirling,*"Divided Saddle Theory: a new idea for rate constant calculation"* **J. Chem. Theor. Comp.** 10 (2014) 1121-1127.