Theses of the doctoral dissertation

Theoretical investigation of the dynamics and microhydration of the $F^- + CH_3I$ S_N2 and proton-transfer reactions

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1. Introduction, theoretical background

The bimolecular nucleophilic substitution (S_N2) reactions are of fundamental importance in organic chemistry. In the case of the S_N2 reactions a nucleophilic attacking agent (which bonds to positive charges) replaces another group called leaving group while connecting to a carbon atom. These reactions are stereospecific, occur with inversion in most cases, which means that the configuration of the product is the opposite to the configuration of the reactant. The oldest mechanism was discovered by *Paul Walden* in 1896. During this so called Walden inversion the nucleophile attacks the reactant to the opposite side relative to the leaving-group side (back side attack), then the reaction takes place with the breaking of the bond between the leaving group and the carbon atom and the formation of a new bond between the nucleophile and the carbon atom. In this way an inversion occurs.

There are retention pathways beside the original Walden-inversion reaction path. Among these reaction pathways the front-side attack mechanism was described firstly. In 2015 Szabó and Czakó discovered a new retention mechanism called double inversion. It is needed to be mentioned that the barrier height of the double inversion is below the barrier height of the front-side attack mechanism by 15 kcal/mol in the case of the $F^- + CH_3Cl$ system. In consequence, the double-inversion mechanism occurs with significantly higher probability than front-side attack, especially at low collision energies. In the first step of the double inversion the attacking agent abstracts a proton from the reactant molecule. After that, this proton forms a new bond on the other side synchronously with the umbrella motion of the other two hydrogens. Thus, the first inversion occurs. The second inversion is a Walden inversion which produces the final retention product. If the second inversion does not take place, a reactant with inverted configuration compared to the initial one is produced. The latter process is the so called induced inversion.

Figure 1 shows the stationary points of the $F^- + CH_3I$ system. Finding the stationary points (minima and transition states) is very important in connection with the investigation of the mechanism of chemical reactions. Minima correspond to the reactants, products and some complexes developed during the reaction, while transition states usually belong to first-order saddle points.

Finding stationary points is important, but not enough to investigate a reaction, because a given reaction (trajectory) does not follow exactly the minimum energy path determined by the stationary points. As a result, carrying out reaction dynamics simulations is necessary. One type of the reaction dynamics simulations is the direct dynamics. Direct dynamics simulations demand significant computational time due to the calculation of the high amount of energy gradients with electronic structure methods. Consequently, few trajectories can be run with direct dynamics simulations and only low-level electronic structure theory can be applied for gradient computations.

The other way in the field of chemical reaction dynamics which I used during my PhD work is based on the development of analytical potential energy surfaces (PES). With this method the energies of the PES points are computed with high-level electronic structure methods. The fitting of the PES points is permutationally invariant to the identical atoms. I run quasiclassical trajectories on the surface which means that the simulations use the laws of the classical physics, but the rotational-vibrational energy of the reactant is set quantum-mechanically. The energy gradients needed for the trajectory simulations are provided by the PES function. This is the reason for the much lower computational cost of this method compared with the direct dynamics method. Due to this low computational cost millions of trajectories can be run at every collision energy. Thus, the results will be statistically more accurate and the method is suitable for finding new low-probability reaction pathways.

There are initial and final conditions in connection with the reaction dynamics simulations. The initial conditions are the sampling of the vibrational energy levels of the reactants and the set-up of the relative position and the relative velocities of the reactants. The final conditions can be obtained from the results of the trajectory simulations. The reaction probabilities, cross sections, the attack angle, the scattering angle, the relative translational energy, the internal energy and the trajectory time distributions belong to the final conditions.

The definition of the reaction probability:

$$P(b) = N_{\text{reactive}}/N_{\text{all}} \,, \tag{1}$$

where N_{reactive} is the number of the reactive trajectories belonging to a given reaction channel, while N_{all} is the number of all the trajectories on a given collision energy and impact parameter (b). Integral cross section is obtained as a b-weighted reaction probability integrated from 0 to b_{max}:

$$\sigma = \int_0^{b\text{max}} 2\pi\, b\, P(b)\mathrm{d}b \,. \tag{2}$$

2. Goals of the research

The primary goal of my research was the theoretical investigation of the dynamics and the mechanism of the $F^- + CH_3I$ reaction. Since analytical potential energy surface was not available for the $F^- + CH_3I$ system, I aimed a development of a high-quality analytical PES for the $F^- + CH_3I$ reaction. This process started with the high-level *ab initio* characterization of the stationary points shown in Figure 1. The analytical PES makes possible performing efficient dynamics simulations. I planned the observation of the retention pathways based on the large number of trajectories.

My further goal was in the case of the $F^- + CH_3I$ reaction the investigation of the vibrational excitation of the methyl-iodide reactant in collaboration with the experimental

research group of Roland Wester in Innsbruck. The newly developed PES is usable for performing mode-specific trajectory simulations. Due to the collaboration the comparison between the results of my computations and those of the experiment is possible. Since the crossed-beam ion-molecule experiment investigates only one vibrational mode (the CH symmetric stretch) and only two collision energies, I aimed studying the effects of all of the vibrational modes at many different collision energies.

The investigation of the front-side complex (FSMIN in Figure 1) in the case of the dynamics of the $F^- + CH_3I$ and the $F^- + CH_3Cl$ S_N2 reactions was among my goals. This minimum may have a particularly important role due to the low electronegativity of the iodine among the halogens. This low electronegativity is the reason for the low relative energy of the complex as seen in Figure 1. This kind of dynamical study was long overdue; now thanks to the newly developed $F^- + CH_3I$ PES this simulation can be carried out.

I aimed at developing and implementing a method which assigns trajectory geometries to stationary points. This project was of high significance because the role of the stationary points was usually observed manually before.

My last goal was the mapping and the accurate *ab initio* characterization of the stationary points of the $F^-(H_2O) + CH_3I$ system. The new stationary points make possible to propose new reaction pathways. I paid particular attention to the double-inversion mechanism in micro-hydrated circumstances, because in the case of this system the water may induce the production of methanol with retention of configuration.

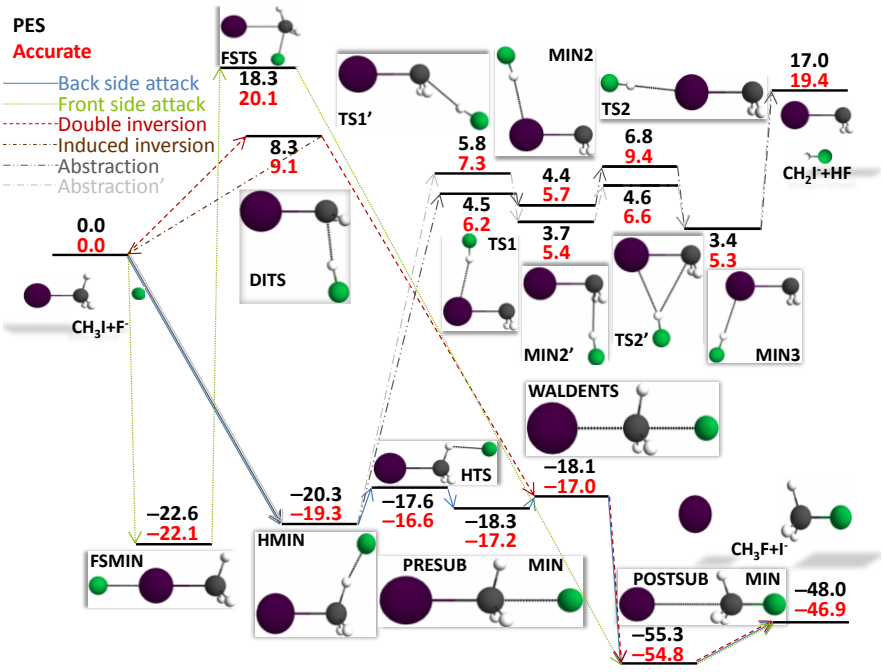

Figure 1. The energy diagram of the $F^- + CH_3I$ reaction; indicating the different reaction pathways, the relative energies (kcal/mol) computed on the potential energy surface (black) and the most accurate relative energies (red)

3. Methods

I used the *MOLPRO* program package for geometry optimization, frequency and energy computations. The analysis of the results of the quasiclassical dynamical simulations and the assignment of the trajectory geometries to stationary points were carried out by self-developed codes written in *FORTRAN 90* language. Beside this I used *shell* and *awk* scripts during my work. In order to fit the points of the potential energy surface and carry out quasiclassical dynamical simulations I used codes which were at our group's disposal. For the visualization of the trajectories the *MacMolPlt* program, while making graphics the *Origin 6* program were used.

The correction of the initial potential energy surface developed for the $F^- + CH_3I$ reaction was carried out by sampling of and adding new points to the next surface from the trajectories which are unphysical at a given collision energy. These trajectories were arised from specific regions of the surface where the PES-function did not contain enough points, and consequently gave very low energy values for these regions. At the end of the development of the surface I checked the trajectories which were possible at the given collision energy, comparing the energies given by the PES function with the *MOLPRO* energies computed at the same level as the PES points were. I calculated the energies of the PES points at *CCSD(T)-F12b/aug-cc-pVTZ(-PP)* level with core corrections calculated at *CCSD(T)/aug-cc-pwCVDZ(-PP)* level. The *CCSD(T)* means high-level electronic structure method which takes the correlated motion of the electrons into account. In the case of the explicitly correlated *F12* methods coordinate system involving electron-electron distances is used instead of Cartesian coordinates. Using *F12* methods good results can be reached with relatively small basis sets. I took into account the scalar relativistic effects for the iodine atom using effective core potential with the proper pseudopotential *(PP)* basis set.

4. Results

T1. I developed a potential energy surface for the $F^- + CH_3I$ reaction and studied the dynamics of the $F^- + CH_3I(v=0)$ reaction [1].

I obtained the final surface by the fitting of 50 496 *ab initio* energy points. I managed to reach an accuracy below 1 kcal/mol in the lower energy regions with the PES fitting error. It is need to be mentioned that the low fitting error in the chemically important regions is required but not surely enough to obtain a good potential energy surface.

Among the results of the quasiclassical trajectory simulations the distributions of the scattering angle and the internal energy showed good agreement with the experiment. I determined above this the reaction energy diagram showed by Figure 1, the geometrical parameters of the stationary points, integral cross sections, reaction probabilities as the function of the impact parameter (opacity functions) and trajectory integration time distributions.

My work reached the goal to find trajectories with double inversion in the case of the F^- + CH_3I system (Figure 1 shows that in the case of this system the barrier height of double inversion is below the barrier height of the front-side attack by 10-11 kcal/mol. As a result, at lower collision energies the double-inversion trajectories are dominant over the front-side attack for this system, too.) I supported the assumption that double-inversion pathways were found with trajectory animations.

T2. I determined the vibrational mode-specific dynamics of the F^- + CH_3I reaction [2,3].

In the case of chemical reactions translational, vibrational, and rotational energy can be given to the reactants. Different reaction pathways can be promoted with excitation of different energy modes. For atom-diatomic molecule collisions the Polanyi rules can be directly applied, which states that in the case of the late-barrier endothermic reactions the excess of the vibrational energy promotes the reaction, while in the case of the early-barrier exothermic reactions addition of translational energy helps the reaction. The Polanyi rules are in accord with the Hammond's postulate which states that the transition states of endothermic reactions are more similar to the products while the transition states of exothermic reactions are more similar to the reactants structurally, because it means that the transition states of endothermic reactions are significantly altered compared with the geometries of the reactants.

Polyatomic systems have different vibrational modes. This means that the Polanyi rules can not be directly applied for these systems, because not all of the vibrational modes have the same effect in the case of a given reaction. For the F^- + CH_3I reaction it was already supposed that the CH symmetric stretching does not promote the substitution significantly, but experimental result was not available to prove this. Our research in collaboration with Roland Wester's innsbrucker research group supported this assumption both theoretically and experimentally, and above this another fact that the abstraction (proton transfer) reaction can be promoted by the excitation of the CH symmetric stretch [2].

The calculated integral cross sections in the case of S_N2 reactions show decreasing tendency with increasing collision energy. This is because the majority of the S_N2 reactions is inversion, which is barrierless and strongly exothermic process in the case of the F^- + CH_3I system, so increasing the collision energy results in that the reactants do not come into reactive orientation, just pass beside each other, especially in the case of higher impact parameters. For the abstraction, induced inversion, and retention processes, which have significant positive barriers, increasing the collision energy enhances the integral cross sections until reaching a certain collision energy. The double inversion (which constitutes the majority of the retention trajectories, except the highest collision energies) and the induced inversion are indirect processes which means that the trajectories belonging to these reaction pathways consist of relatively many steps. In contrast, the abstraction is usually a direct, quick reaction. The indirect processes do not favour the highest collision energies,

because the large energy causes a high probability for the fragmentation of the system, so the reaction has a little chance to occur. For example, the occurence of abstraction is likely instead of double inversion or induced inversion. In consequence, the medium collision energies (10-20 kcal/mol) are the most favourable for the double inversion and induced inversion, while for the abstraction I calculated the largest integral cross sections in the case of the highest collision energies.

The other study in connection with the vibrational excitations is a theoretical work about the effects of excitation of all vibrational modes of the reactant at several collision energies [3]. The investigation showed based on the integral cross section curves that the excitation of the CI stretch promotes the S_N2 inversion most efficiently, and the excitation of the CH symmetric stretch promotes efficiently also the double inversion beside the abstraction. This is not surprising because the first step of the double-inversion process is an abstraction.

T3. We uncovered the role of the front-side minimum of the $F^- + CH_3I$ system in the reaction [4].

I mentioned in the introduction that in the case of the $F^- + CH_3I$ system the front-side complex has prominent role. We showed with István Szabó for the first time quantitatively that for the $F^- + CH_3I$ system the formation of long-lived front-side complexes is significantly more prevalent than in the case of the $F^- + CH_3Cl$ system. Beside this in the $F^- + CH_3I$ reaction the formation of the front-side complex from a trajectory starting with back-side attack is also typical.

T4. I worked out and applied a method for the assignment of trajectory points to stationary-point geometries in the case of the $F^- + CH_3I$ reaction [5].

I implemented an Eckart-transformation based method, which assigns trajectory geometries to stationary points. The application of the new method and program also showed the important role of the front-side minimum. This study revealed that the trajectories spend the majority of time in the neighbourhood of the hydrogen-bonding minimum (HMIN), which is not surprising due to the low energy of this complex as seen in Figure 1. The important role of the postsubstitution minimum (POSTMIN) can be explained similarly. These informations are showed by the figures showing the probabilities of the assigments to the different stationary points. The diagrams showing the deviations of the stationary points from trajectory points were also important. I also studied an orthogonal trajectory projection [4], on which I projected the position of the fluoride ion to one plane of the methyl-iodide. I determined above this novel stationary point transition matrices showing the probabilities of transitions between different stationary points. Lastly I studied the time dependency of the assigned stationary points in the case of some representative trajectories.

T5. I carried out the most detailed and most accurate mapping of the stationary points of the $F^-(H_2O) + CH_3I$ system and I proposed a new water-induced double-inversion reaction pathway [6].

I determined and discussed 29 stationary points and reaction energy diagrams constructed from these stationary points during my work in connection with the $F^-(H_2O) + CH_3I$ system. The stationary points were found based on earlier studies, own chemical intuition, and minimum energy path calculations. I suggested five different reaction pathways. Three of these are the microhydrated versions of *Walden*-inversion, double inversion, and front-side attack pathways of the nonhydrated system. In the case of the other two reaction routes the water molecule or the hydroxide ion are the reactants. In one of the latter cases hydroxide ion forms from the reaction between the fluoride ion and the water molecule then the hydroxide ion inverts the methyl-iodide. The other is the water-induced double-inversion pathway which starts with a proton abstraction by the fluoride ion. After that, the water molecule donates a proton to the opposite side to the splitted proton. In that way, the first inversion is occurred. Finally, with the formed OH^- ion a *Walden*-inversion occurs, and with two inversions methanol is produced with retention.

5. Publications and conference participations

5.1. Publications directly related to the topic of the dissertation

1. High-level *ab initio* potential energy surface and dynamics of the F^- + CH_3I S_N2 and proton-transfer reaction
   B. Olasz, I. Szabó, G. Czakó
   Chem. Sci., 2017, 8, 3164-3170
   IF_{2017}: 9.063
   Number of independent references: 8
2. Stretching vibration is a spectator in nucleophilic substitution
   M. Stei, E. Carrascosa, A. Dörfler, J. Meyer, B. Olasz, G. Czakó, A. Li, H. Guo, R. Wester
   Sci. Adv., 2018, 4, eaas9544
   IF_{2017}: 11.511
   Number of independent references: 3
3. Mode-specific quasiclassical dynamics of the F^- + CH_3I S_N2 and proton-transfer reactions
   B. Olasz, G. Czakó
   J. Phys. Chem. A, 2018, 122, 8143-8151
   IF_{2017}: 2.836
   Number of independent references: 0
4. Deciphering front-side complex formation in S_N2 reactions via dynamics mapping
   I. Szabó, B. Olasz, G. Czakó
   J. Phys. Chem. Lett., 2017, 8, 2917-2923
   IF_{2017}: 8.709
   Number of independent references: 10
5. Uncovering the role of the stationary points in the dynamics of the F^- + CH_3I reaction
   B. Olasz, G. Czakó
   Phys. Chem. Chem. Phys., 2019, 21, 1578-1586
   IF_{2017}: 3.906
   Number of independent references: 0
6. High-level-optimized stationary points for the $F^-(H_2O)$ + CH_3I system: Proposing a new water-induced double-inversion pathway
   B. Olasz, G. Czakó
   J. Phys. Chem. A, 2019, 123, 454−462
   IF_{2017}: 2.836
   Number of independent references: 1

5.2. Publication not utilized but related to the dissertation

1. Effects of the level of electronic structure theory on the dynamics of the F^- + CH_3I reaction
   T. Győri, B. Olasz, G. Paragi, G. Czakó
   J. Phys. Chem. A, 2018, 122, 3353−3364
   IF_{2017}: 2.836
   Number of independent references: 3

5.3. Publications not directly related to the topic of the dissertation, patent

1. Synthesis, characterization, and electrocatalytic properties of a custom-designed conjugated polymer with pyridine side chain
   D. Hursán, G. London, B. Olasz, C. Janáky
   Electrochim. Acta, 2016, 217, 92-99
   IF_{2016}: 4.798
   Number of independent references: 2
2. Continuous-flow solid-phase peptide synthesis: A revolutionary reduction of the amino acid excess
   I. M. Mándity, B. Olasz, S. B. Ötvös, F. Fülöp
   ChemSusChem, 2014, 7, 3172-3176
   IF_{2014}: 7.657
   Number of independent references: 18
3. Continuous-flow solid-phase peptide synthesis: A revolutionary reduction of the amino acid excess
   I. M. Mándity, B. Olasz, S. B. Ötvös, F. Fülöp
   J. Pept. Sci., 2014, 20, S57-S57
   IF_{2014}: 1.546
   Number of independent references: 0
4. Continuous flow peptide synthesis
   F. Fülöp, I. Mándity, B. Olasz
   Registration number: WO2015128687 A1
   Year of publishing: 2015
   International patent

5.4. Conference participations

1. Highly efficient peptide synthesis
   Balázs Olasz
   XXXII. National Scientific Student Conference
   Budapest, 2015 (oral lecture)

2. Theoretical study of the dynamics and microsolvation of the F^- + CH_3I reaction
   Balázs Olasz
   XLI Chemical lecturer days
   Szeged, 2018 (oral lecture)

3. Theoretical study of the dynamics and microsolvation of the F^- + CH_3I reaction
   Balázs Olasz, Gábor Czakó
   MTA Reaction Kinetics and Photochemistry Working Group Meeting
   Veszprém, 2018 (oral lecture)

Publications in scientific journals

Related to the dissertation: 7	Total: 10

Cumulated impact factor

Related to the dissertation: 41,697	Total: 55,698

Cumulated independent citation

Related to the dissertation: 25	Total: 45