Curriculum vitae et studiorum

Klaudia Mráziková

Web of Science Researcher ID: AAY-5483-2021
Address:
Telephone Number:

Scientific background:

I am a researcher in computational chemistry. I have experience with quantum chemical methods, hybrid quantum mechanics/molecular mechanics (QM/MM) methods, molecular mechanics and atomistic molecular dynamics simulations applied on different types of molecular systems. I use quantum chemistry to study chemical reactions and reaction mechanisms in the field of planetary chemistry, prebiotic chemistry and astrochemistry. Furthermore, I study non-covalent interactions operating in nucleic acids with focus on their physico-chemical origin and on evaluation of biomolecular force-fields. Finally, I use high-level quantum chemistry to study intermolecular interactions of molecular systems under the influence of external electric field.

EDUCATION:

Diploma of doctorate in "Biomolecular Chemistry and Bioinformatics". 23/07/2018-14/06/2023

- Title: "Computer Modeling of Nucleic Acids Using Quantum Chemistry and Force-Fields"
- Supervisor: Prof. Jiří Šponer
- Score: Excellent
- Delivered Date: 14/06/2023
- Diploma is delivered from Faculty of Science of Masaryk University

Department of Structure and Dynamics of Nucleic Acids, National Centre for Biomolecular Research, Masaryk University – Brno, Czech Republic

I elaborated my doctoral thesis at Masaryk University in collaboration with the Institute of Biophysics of the Czech Academy of Sciences. I studied physico-chemical aspects of nucleic acids using state-of-the-art quantum mechanics (QM) methods with focus on specific molecular interactions and on evaluation of molecular mechanics (MM) in reproducing them. The investigated items were especially two kinds of recurrent non-covalent interactions, lone-pair...π (lp···π) and phosphate...π, and nucleic acids containing them, particularly UNCG (U = uracil, N = any nucleotide, C = cytosine, G = guanine) and GNRA (R = nucleotide with purine base, A = adenine) RNA tetraloops, and Z-DNA. These motifs are particularly challenging for structural description by MM, i.e., biomolecular force-fields, during molecular dynamics (MD) simulations. We published the results described in my doctoral thesis in 5 research articles in journals with IF, while I am the first author for three of them.

The results are summarized as follows. We elucidated the origin of short contact distances in the lp···π interaction of Z-DNA. We first excluded the presence of stabilizing orbital interactions by revealing the nature of the lp···π interaction availing SAPT analysis. The SAPT profile of the lp···π interaction corresponds to typical non-covalent interactions. Then, we showed that these short distances cannot be facilitated solely by the lp···π interaction since highly-accurate double-hybrid DFT with empirical D3 dispersion correction (DHDF-D3) interaction energy scans showed that the optimal distances overestimate the distances observed in crystal structures. Finally, we found that stereochemical effects cause the compression of this interaction, hence they are the driving force of the short lp···π distances. An unexpected outcome of this work is the notification that the standard carbon vdW radius defining sub-vdW contacts is inappropriate for sp2 carbon atoms. The fact that individual nucleobase carbon atoms have different effective volumes, as indicated by atom-in-molecule DFT-D4 polarizabilities, has implications for force-fields parametrization of non-bonding terms. Then, we recognized multiple inaccuracies related to the problematic description of the UUCG RNA tetraloop by the OL3 AMBER force-field. We utilized large-scale QM/MM geometry optimizations and QM interaction and conformational energy scans to individually analyze each of these inaccuracies consisting of signature hydrogen bonds, backbone or ribose dihedrals and the lp···π interaction. None of the corrections tested in MD simulations lead to substantial improvement of the folded/unfolded ratio of the UUCG RNA tetraloop. This work demonstrated how difficult it is to parameterize RNA force-fields. One correction can lead to problems in another part of the molecule since these discrepancies are coupled and eventually error-compensate themselves. The UUCG RNA tetraloop possesses a uniquely tight conformation without sufficient flexibility to evade the individual imbalances. A detailed look at the lp···π interaction with AMBER force-field exposed that this contact is improperly described in the short-range distance region (≤2.9 Å). The overly repulsive short-range region is a well-known and inherent feature of the r^{-12} term of the LJ potential. Simultaneously, minima of the interaction energy curves are significantly shifted to larger distances. Sampling of the large repulsive forces in MD simulations of the lp···π containing systems like Z-DNA and UNCG RNA tetraloop likely contributes to the disruption of their native states. The important outcome of this article is the notification that LJ parameters for the nucleobase atoms, especially carbons, should be revised in the AMBER force-field since LJ radii for some of them are apparently too large. Further works focused on (thio)phosphate···π interaction in the U-turn motif of the Neomycin-sensing riboswitch (NSR) and GNRA RNA tetraloop systems. In the NSR, the phosphate forming the phosphate···π contact interacts with the uracil nucleobase (OP2···U) while in the GNRA RNA tetraloop it interacts with the guanine nucleobase (OP2···G). For the former, the computations on the phosphorothioated NSR revealed contradictory demands on the LJ parameters for the SP2 atom when forming the individual U-turn signature interactions, either the hydrogen bond or the thiophosphate···π interaction. It suggests that there is no ideal universal set of the LJ parameters for the SP2 atom. In both U-turn systems, the AMBER force-field underestimates the strength of the phosphate···π and thiophosphate···π interaction due to the missing polarization which is an important stabilizing contributor to this interaction. Yet, for the OP2···G the AMBER force-field interaction energy is even destabilizing, apparently contributing to imbalances between the folded and unfolded states of the GNRA RNA tetraloop in MD simulations. Furthermore, the AMBER force-field exaggerates the phosphate···π and thiophosphate···π optimal distances similarly to lp···π. The AMBER force-field issues for lp···π and phosphate···π interactions differ, hence the suggested corrections are also unalike. While for the former the decrease of the LJ radii for some of the nucleobase carbons could be sufficient, the latter requires the addition of the correction term stabilizing the phosphate···π interaction. Understanding the interactions in biomolecules is helpful for force-field development. Our works bring insight into the physical nature of the lp···π and phosphate···π interactions. We identified particular interaction energy terms responsible for their improper description and suggested future directions of the AMBER force-field development. At this stage, it seems necessary to include structure-specific corrections to the existing AMBER force-field potentials to attain the required simulation outcome of particular nucleic acid systems.

Competence: QM methods: ab initio methods (coupled-cluster, MP2), DFT (hybrid, double-hybrid, low-composite methods), SAPT; hybrid QM/MM methods; MM: AMBER force-field; MD

Diploma of master in “Biomolecular Chemistry”. 21/07/2016-22/06/2018

- Title: “A Study of Molecular Interactions in Nucleic Acids: Sugar-Base and Phosphate-Base Stacking”
- Supervisor: Prof. Jiří Šponer
- Consultant: Dr. Holger Kruse
- Score: Excellent
- Delivered Date: 22/06/2018
- Diploma is delivered from Faculty of Science of Masaryk University

Department of Structure and Dynamics of Nucleic Acids, National Centre for Biomolecular Research, Masaryk University – Brno, Czech Republic

I elaborated my thesis at Masaryk University in collaboration with the Institute of Biophysics of the Czech Academy of Sciences. The aim of the thesis was firstly to use state-of-the-art QM methods for verifying the short distances between oxygen atom and nucleobase resulting in oxygen-π contact as found in crystallographic structures of Z-DNA/RNA and RNA U-turns. Secondly, to study these short distances and to perform MM in order to validate reliability of MD simulations for these systems. We used small models of DME(dimethylether)/DMP(dimethyl phosphate) and nucleobase and computed their PES. We performed high-order SAPT analysis and found that the stabilization of the DME...nucleobase stacking (lone-pair...π interaction) stems mostly from London dispersion and to a lesser degree from electrostatics. In the DMP...nucleobase stacking (phosphate…π interaction) the London dispersion, induction (polarization) and electrostatics are almost equally important for the stabilization with only a slight predominance of the London dispersion. We used the highly-accurate double-hybrid density functional DSD-BLYP-D3(BJ) with the ma-def2-QZVP basis set for energy scans above the nucleobase with DME or DMP as a molecular probe. We analyzed the optimal distances between the oxygen atom and the nucleobase, and the corresponding interaction energies. Then, we performed MM (AMBER force-field) calculations and compared them with QM results. The non-bonded term of AMBER force-field is over-repulsive at short distances for this interaction, which leads to longer DME...nucleobase distances and smaller stabilization. It appears to be strongly dominated by the LJ potential.

Diploma of bachelor in “Biochemistry”. 17/07/2013-13/06/2016

- Title: “Study of microRNAs Expression in Body Fluids Using Digital PCR”
- Supervisor: Prof. Ondřej Slabý
- Consultant: Dr. Jaroslav Juráček
- Score: Excellent
- Delivered Date: 13/06/2016
- Diploma is delivered from Faculty of Science of Masaryk University

PARTICIPATION TO SCHOOLS:

Virtual Winter School on Computational Chemistry – online

Date: 21 – 25 February 2022

WORKING EXPERIENCE:

Research group led by Dr. Giuseppe Cassone, position: **postdoc**, 15/07/2024-present
Role: QM investigation of SO_2 formation in exoplanets' atmospheres
Computational Modelling Laboratory, Institute for Physical-Chemical Processes of National Research Council of Italy (IPCF-CNR)

I have been working as a postdoc in the field of quantum chemistry and planetary chemistry. During this still on-going project we have been investigating chemical reactions leading to formation of SO_2 in atmospheres of exoplanets like WASP-39b, WASP-107b and GJ3470b. Then, we studied chemical reactions of CS_2 and OCS under asteroid impacts on young exoplanets. These works have not been published yet. Additionally, we used quantum chemistry to assess the effect of external electric fields on prototypical hydrogen-bonded dimers. The results are summarized in two journal articles (one published and one accepted) with titles "Water Dimer under Electric Fields: An Ab Initio Investigation up to Quantum Accuracy" and "Hydrogen Bonds under Electric Fields with Quantum Accuracy" where for the latter I am one of the three first-authors.

Research group led by Dr. Martin Ferus, position: **postdoc**, 16/01/2023-31/12/2023
Role: QM investigation of chemical reactions leading to phosphine in Venus' atmosphere
Department of Spectroscopy, J. Heyrovský Institute of Physical Chemistry of the Czech Academy of Sciences

I was working as a postdoc in a laboratory led by Dr. Martin Ferus in the field of astrochemistry. In collaboration with scientists from the Institute for Physical-Chemical Processes, National Research Council of Italy (IPCF-CNR) in Messina and from the Department of Earth Sciences at Cambridge University we investigated abiotic pathways leading to phosphine presence in Venus' atmosphere. Using quantum chemistry and considering atmospheric conditions of Venus we predicted a possible reaction route and described reaction mechanisms leading from the formyl radical and phosphorous monoxide to phosphine. The computations involved analyses of molecular vibrations necessary to define minima on potential energy surfaces, transition structures searches and thermochemistry. The results are written in the already accepted paper in the *Astrobiology* journal with title "A novel abiotic pathway for phosphine synthesis over acidic dust in Venus' atmosphere".

Research group led by Prof. Jiří Šponer, position: **doctoral student**, 01/08/2017-30/06/2023
Role: Studies of prebiotic molecules and chemical reactions by quantum-chemical methods
Department of Structure and Dynamics of Nucleic Acids, Institute of Biophysics of the Czech Academy of Sciences

I was working in a laboratory of computational biochemists led by Prof. Jiří Šponer in the field of nucleic acids. Besides the research work related to my doctoral studies, I was working on chemical reactions and reaction mechanisms in the field of origin of life and co-authored three publications: "High-Energy Proton-Beam-Induced Polymerization/Oxygenation of Hydroxynaphthalenes on Meteorites and Nitrogen Transfer from Urea: Modeling Insoluble Organic Matter?" published in *Chemistry – A European Journal*, "Prebiotic Route to Thymine from Formamide-A Combined Experimental-Theoretical Study" published in *Molecules* and "Formamide-Based Post-impact Thermal Prebiotic Synthesis in Simulated Craters: Intermediates, Products and Mechanism" published in *Frontiers in Astronomy and Space Sciences*.

PROJECTS PARTICIPATION

Exo-planetary Cloudy Atmospheres and Stellar High energy (Exo-CASH), position: **postdoc**
Role: QM investigations of chemical species in exoplanets' atmospheres, 15/07/2024-present
Institute for Physical-Chemical Processes of National Research Council of Italy (IPCF-CNR)

Structural gymnastics of nucleic acids: from molecular principles through biological functions to therapeutic targets. Support of integrated research team. (SYMBIT), position: **doctoral student**
Role: Studies of nucleic acids using quantum chemistry, 01/09/2021-31/10/2022
Institute of Biophysics of the Czech Academy of Sciences

PUBLICATIONS:

1) Hydrogen Bonds under Electric Fields with Quantum Accuracy.
   Amadeo, A.; Torre, M. F.; Mráziková, K.; Saija, F.; Trusso, S.; Xie, J.; Tommasini, M.; Cassone, G.
   Journal of Physical Chemistry A **2025**, *Accepted*

   Abstract: Hydrogen bonds (H-bonds) are pivotal in various chemical and biological systems and exhibit complex behavior under external perturbations. This study investigates the structural, vibrational, and energetic properties of prototypical H-bonded dimers – water $(H_2O)_2$, hydrogen fluoride $(HF)_2$, hydrogen sulfide $(H_2S)_2$, and ammonia $(NH_3)_2$ – and the respective monomers under static and homogeneous electric fields (EFs) using accurate explicitly correlated singles and doubles coupled cluster method (CCSD) for equilibrium geometries and harmonic vibrational frequencies, and the perturbative triples CCSD(T) method for energies. As for the vibrational response of the H_2O, HF, H_2S, and NH_3 monomers, it turns out that dipole derivatives primarily govern geometry relaxation. Perturbation theory including cubic anharmonicity can reproduce CCSD results on the vibrational Stark effect, except for NH_3, where deviations arise due to its floppiness. The field-induced modifications in H-bond lengths, vibrational Stark effects, binding energies, and charge-transfer mechanisms in monomers and dimers are elucidated. Symmetry-adapted perturbation theory (SAPT) analysis on dimers reveals that electrostatics dominate the stabilization of H-bonds across all field strengths, while induction contributions increase significantly with stronger fields, particularly in systems with more polarizable atoms. Our results reveal a universal strengthening of intermolecular interactions at moderate to strong field intensities, with significant variability among dimers due to inherent differences in molecular polarizability and charge distribution. Notably, a direct correlation is observed between the binding energies and the vibrational Stark effect of the stretching mode of the H-bond donor molecule, both in relation to the charge-transfer energy term, across all the investigated dimers. All these findings provide insights into the EF-driven modulation of H-bonds, highlighting implications for catalysis, hydrogen-based technologies, and biological processes.

2) Water Dimer under Electric Fields: An Ab Initio Investigation up to Quantum Accuracy.
   Torre, M. F.; Amadeo, A.; Cassone, G.; Tommasini, M.; Mráziková, K.; Saija, F.
   Journal of Physical Chemistry A **2024**, *128* (28), 5490–5499. DOI: 10.1021/acs.jpca.4c01553

   Abstract: It is well-established that strong electric fields (EFs) can align water dipoles, partially order the H-bond network of liquid water, and induce water splitting and proton transfers. To illuminate the fundamental behavior of water under external EFs, we present the first benchmark, to the best of our knowledge, of DFT calculations of the water dimer exposed to intense EFs against coupled cluster calculations. The analyses of the vibrational Stark effect and electron density provide a consistent picture of the intermolecular charge transfer effects driven along the H-bond by the increasing applied field at all theory levels. However, our findings prove that at extreme field regimes (∼1–2 V/Å) DFT calculations significantly exaggerate by ∼10–30% the field-induced strengthening of the H-bond, both within the GGA, hybrid GGA, and hybrid meta-GGA approximations. Notably, a linear correlation emerges between the vibrational Stark effect on OH stretching and H-bond strengthening: a 1 kcal mol^{-1} increase corresponds to an 80 cm^{-1} red-shift in OH stretching frequency.

3) A novel abiotic pathway for phosphine synthesis over acidic dust in Venus' atmosphere.
Mrázikova, K.; Knížek, A.; Saeidfirozeh, H.; Petera, L.; Civiš, S.; Saija, F.; Cassone, G.; Rimmer, P.B.; Ferus, M.
Astrobiology **2024**, *24* (4), 1531-1074 DOI: 10.1089/ast.2023.0046

Abstract: Recent ground-based observations of Venus have detected a single spectral feature consistent with phosphine (PH_3) in the middle atmosphere, a gas which has been suggested as a biosignature on rocky planets. The presence of PH_3 in the oxidized atmosphere of Venus has not yet been explained by any process. However, state-of-the-art experimental and theoretical research published in previous works demonstrated the photochemical origin of another hydride – methane – from carbon dioxide over acidic mineral surfaces on Mars. The production of methane includes formation of the HC·O radical. Our Density Functional Theory (DFT) calculations predict an energetically plausible reaction network leading to PH_3, involving either HC·O or H· radicals. We suggest that, similarly to the photochemical formation of methane over acidic minerals already discussed for Mars, the origin of PH_3 in the Venus' atmosphere could be explained by radical chemistry starting with the reaction of ·PO with HC·O, the latter being produced by reduction of CO_2 over acidic dust in upper atmospheric layers of Venus by ultraviolet radiation. HPO, $H_2P{\cdot}O$, and $H_3P{\cdot}OH$ have been identified as key intermediate species in our model pathway for phosphine synthesis.

4) Multiscale Modeling of Phosphate··· π Contacts in RNA U-Turns Exposes Differences between Quantum-Chemical and AMBER Force Field Descriptions.
Mrázikova, K.; Kruse, H.; Mlýnský, V.; Auffinger, P.; Šponer, J.
Journal of Chemical Information and Modeling **2022**, *62* (23), 6182-6200. DOI: 10.1021/acs.jcim.2c01064

Abstract: Phosphate···π, also called anion···π, contacts occur between nucleobases and anionic phosphate oxygens (OP2) in r(GNRA) and r(UNNN) U-turn motifs (N = A,G,C,U; R = A,G). These contacts were investigated using state-of-the-art quantum-chemical methods (QM) to characterize their physicochemical properties and to serve as a reference to evaluate AMBER force field (AFF) performance. We found that phosphate···π interaction energies calculated with the AFF for dimethyl phosphate···nucleobase model systems are less stabilizing in comparison with double-hybrid DFT and that minimum contact distances are larger for all nucleobases. These distance stretches are also observed in large-scale AFF vs QM/MM computations and classical molecular dynamics (MD) simulations on several r(gcGNRAgc) tetraloop hairpins when compared to experimental data extracted from X-ray/cryo-EM structures (res. ≤ 2.5 Å) using the WebFR3D bioinformatic tool. MD simulations further revealed shifted OP2/nucleobase positions. We propose that discrepancies between the QM and AFF result from a combination of missing polarization in the AFF combined with too large AFF Lennard-Jones (LJ) radii of nucleobase carbon atoms in addition to an exaggerated short-range repulsion of the r^{-12} LJ repulsive term. We compared these results with earlier data gathered on lone pair···π contacts in CpG Z-steps occurring in r(UNCG) tetraloops. In both instances, charge transfer calculations do not support any significant n → π* donation effects. We also investigated thiophosphate···π contacts that showed reduced stabilizing interaction energies when compared to phosphate···π contacts. Thus, we challenge suggestions that the experimentally observed enhanced thermodynamic stability of phosphorothioated r(GNRA) tetraloops can be explained by larger London dispersion.

5) Formamide-Based Post-impact Thermal Prebiotic Synthesis in Simulated Craters: Intermediates, Products and Mechanism.
Ferus, M.; Knížek, A.; Petera, L.; Pastorek, M.; Hrnčířová, J.; Jankovič, L.; Ivanek, O.; Šponer, J.; Křivková, A.; Saeidfirozeh, H.; Civiš, S.; Chatzitheodoridis, E.; Mrázikova, K.; Nejdl, L.; Saija, F.; Šponer, J. E.; Cassone, G.
Frontiers in Astronomy and Space Sciences **2022**, *9*. DOI: 10.3389/fspas.2022.882145.

Abstract: Influx of matter from impacting meteoroids and hydrothermal crater weathering are important factors modifying the rock and mineral inventory of young planets undergoing heavy bombardment. These processes may have influenced not only the geochemical environment of, e.g., early Mars and other planets, but also the peculiar prebiotic chemistry on early Earth. Here, we present a synergistic experimental and computational investigation of the intermediates of chemical reactions of the formamide-based synthesis of canonical and non-canonical nucleobases by thermochemistry in hot hydrothermal crater environments. We put our findings into context with previously investigated plasma-initiated synthesis occurring directly during impact. Both processes result into the formation of all canonical nucleobases, hypoxanthine, purine, and into the onset of the simplest amino acid glycine. Furthermore, it turns out that radical species such as CN and H play a key role in the plasma-assisted impact chemistry. However, post-impact thermochemistry is essential for the origin of formamidine and 2-aminoacetonitrile, intermediate species detected in this study by means of FTIR spectroscopy.

6) Short-Range Imbalances in the AMBER Lennard-Jones Potential for (Deoxy)Ribose···Nucleobase Lone-Pair···π Contacts in Nucleic Acids.
Mráziková, K.; Sponer, J.; Mlynsky, V.; Auffinger, P.; Kruse, H.
Journal of Chemical Information and Modeling **2021**, *61* (11), 5644-5657. DOI: 10.1021/acs.jcim.1c01047

Abstract: The lone-pair···π (lp···π) (deoxy)ribose···nucleobase stacking is a recurring interaction in Z-DNA and RNAs that is characterized by sub-van der Waals lp···π contacts (<3.0 Å). It is a part of the structural signature of CpG Z-step motifs in Z-DNA and r(UNCG) tetraloops that are known to behave poorly in molecular dynamics (MD) simulations. Although the exact origin of the MD simulation issues remains unclear, a significant part of the problem might be due to an imbalanced description of nonbonded interactions, including the characteristic lp···π stacking. To gain insights into the links between lp···π stacking and MD, we present an in-depth comparison between accurate large-basis-set double-hybrid Kohn−Sham density functional theory calculations DSD-BLYP-D3/ma-def2-QZVPP (DHDF-D3) and data obtained with the nonbonded potential of the AMBER force field (AFF) for NpN Z-steps (N = G, A, C, and U). Among other differences, we found that the AFF overestimates the DHDF-D3 lp$\cdots\pi$ distances by ∼0.1−0.2 Å, while the deviation between the DHDF-D3 and AFF descriptions sharply increases in the short-range region of the interaction. Based on atom-in-molecule polarizabilities and symmetry-adapted perturbation theory analysis, we inferred that the DHDF-D3 versus AFF differences partly originate in identical nucleobase carbon atom Lennard-Jones (LJ) parameters despite the presence/absence of connected electron-withdrawing groups that lead to different effective volumes or vdW radii. Thus, to precisely model the very short CpG lp$\cdots\pi$ contact distances, we recommend revision of the nucleobase atom LJ parameters. Additionally, we suggest that the large discrepancy between DHDF-D3 and AFF short-range repulsive part of the interaction energy potential may significantly contribute to the poor performances of MD simulations of nucleic acid systems containing Z-steps. Understanding where, and if possible why, the point-charge-type effective potentials reach their limits is vital for developing next-generation FFs and for addressing specific issues in contemporary MD simulations.

7) Prebiotic Route to Thymine from Formamide-A Combined Experimental-Theoretical Study.
Petera, L.; Mrazikova, K.; Nejdl, L.; Zemankova, K.; Vaculovicova, M.; Pastorek, A.; Civis, S.; Kubelik, P.; Heays, A.; Cassone, G.; Sponer, J.; Ferus, M.; Sponer, J.
Molecules **2021**, *26* (8), 2248. DOI: 10.3390/molecules26082248

Abstract: Synthesis of RNA nucleobases from formamide is one of the recurring topics of prebiotic chemistry research. Earlier reports suggest that thymine, the substitute for uracil in DNA, may also be synthesized from formamide in the presence of catalysts enabling conversion of formamide to formaldehyde. In the current paper, we show that to a lesser extent conversion of uracil to thymine may occur even in the absence of catalysts. This is enabled by the presence of formic acid in the reaction mixture that forms as the hydrolysis product of formamide. Under the reaction conditions of our study, the disproportionation of formic acid may produce formaldehyde that hydroxymethylates uracil in the first step of the conversion process. The experiments are supplemented by quantum chemical modeling of the reaction pathway, supporting the plausibility of the mechanism suggested by Saladino and coworkers.

8) Phosphorothioate Substitutions in RNA Structure Studied by Molecular Dynamics Simulations, QM/MM Calculations, and NMR Experiments.
Zhang, Z.; Vögele, J.; Mrázíková, K.; Kruse, H.; Cang, X.; Wöhnert, J.; Krepl, M.; Šponer, J.
J. Phys. Chem. B **2021**, *125* (3), 825–840. DOI: 10.1021/acs.jpcb.0c10192

Abstract: Phosphorothioates (PTs) are important chemical modifications of the RNA backbone where a single nonbridging oxygen of the phosphate is replaced with a sulfur atom. PT can stabilize RNAs by protecting them from hydrolysis and is commonly used as a tool to explore their function. It is, however, unclear what basic physical effects PT has on RNA stability and electronic structure. Here, we present molecular dynamics (MD) simulations, quantum mechanical (QM) calculations, and NMR spectroscopy measurements, exploring the effects of PT modifications in the structural context of the neomycin-sensing riboswitch (NSR). The NSR is the smallest biologically functional riboswitch with a well-defined structure stabilized by a U-turn motif. Three of the signature interactions of the U-turn: an H-bond, an anion−π interaction, and a potassium binding site; are formed by RNA phosphates, making the NSR an ideal model for studying how PT affects RNA structure and dynamics. By comparing with high-level QM calculations, we reveal the distinct

physical properties of the individual interactions facilitated by the PT. The sulfur substitution, besides weakening the direct H-bond interaction, reduces the directionality of H-bonding while increasing its dispersion and induction components. It also reduces the induction and increases the dispersion component of the anion−π stacking. The sulfur force-field parameters commonly employed in the literature do not reflect these distinctions, leading to the unsatisfactory description of PT in simulations of the NSR. We show that it is not possible to accurately describe the PT interactions using one universal set of van der Waals sulfur parameters and provide suggestions for improving the force-field performance.

9) UUCG RNA Tetraloop as a Formidable Force-Field Challenge for MD Simulations.
Mráziková, K.; Mlýnský, V.; Kührová, P.; Pokorná, P.; Kruse, H.; Krepl, M.; Otyepka, M.; Banáš, P.
J. Chem. Theory Comput. **2020**, *16*, 7601–7617. DOI: 10.1021/acs.jctc.0c00801

Abstract: Explicit solvent atomistic molecular dynamics (MD) simulations represent an established technique to study structural dynamics of RNA molecules and an important complement for diverse experimental methods. However, performance of molecular mechanical (MM) force fields (ff's) remains far from satisfactory even after decades of development, as apparent from a problematic structural description of some important RNA motifs. Actually, some of the smallest RNA molecules belong to the most challenging systems for MD simulations and, among them, the UUCG tetraloop is saliently difficult. We report a detailed analysis of UUCG MD simulations, depicting the sequence of events leading to the loss of the UUCG native state during MD simulations. The total amount of MD simulation data analyzed in this work is close to 1.3 ms. We identify molecular interactions, backbone conformations, and substates that are involved in the process. Then, we unravel specific ff deficiencies using diverse quantum mechanical/molecular mechanical (QM/MM) and QM calculations. Comparison between the MM and QM methods shows discrepancies in the description of the 5′-flanking phosphate moiety and both signature sugar−base interactions. Our work indicates that poor behavior of the UUCG tetraloop in simulations is a complex issue that cannot be attributed to one dominant and straightforwardly correctable factor. Instead, there is a concerted effect of multiple ff inaccuracies that are coupled and amplifying each other. We attempted to improve the simulation behavior by some carefully tailored interventions, but the results were still far from satisfactory, underlying the difficulties in development of accurate nucleic acid ff's.

10) High-Energy Proton-Beam-Induced Polymerization/Oxygenation of Hydroxynaphthalenes on Meteorites and Nitrogen Transfer from Urea: Modeling Insoluble Organic Matter?
Bizzarri, B. M.; Manini, P.; Lino, V.; d'Ischia, M.; Kapralov, M.; Krasavin, E.; Mráziková, K.; Šponer, J.; Šponer, J. E.; Di Mauro, E.; Saladino, R.
Chem. - A Eur. J. **2020**, *26* (65), 14919–14928. DOI: 10.1002/chem.202002318

Abstract: Formation and structural modification of oxygenated polycyclic aromatic hydrocarbons (oxyPAHs) by UV irradiation on minerals have recently been proposed as a possible channel of PAH transformation in astrochemical and prebiotic scenarios of possible relevance for the origin of life. Herein, it is demonstrated that high-energy proton-beam irradiation in the presence of various meteorites, including stony iron, achondrite, and chondrite types, promotes the conversion of two representative oxyPAH compounds, 1-naphthol and 1,8-dihydroxynaphthalene, to complex mixtures of oxygenated and oligomeric derivatives. The main identified products include polyhydroxy derivatives, isomeric dimers encompassing benzofuran and benzopyran scaffolds, and, notably, a range of quinones and perylene derivatives. Addition of urea, a prebiotically relevant chemical precursor, expanded the range of identified species to include, among others, quinone diimines. Proton-beam irradiation of oxyPAH modulated by nitrogen-containing compounds such as urea is proposed as a possible contributory mechanism for the formation and processing of insoluble organic matter in meteorites and in prebiotic processes.

11) Short but Weak: The Z-DNA Lone-Pair···π Conundrum Challenges Standard Carbon Van Der Waals Radii.
Kruse, H.; <u>Mrazikova, K.</u>; D'Ascenzo, L.; Sponer, J.; Auffinger, P.
Angew. Chemie - Int. Ed. **2020**, *59* (38), 16553–16560. DOI: 10.1002/anie.202004201

Abstract: Current interest in lone-pair···π (lp···π) interactions is gaining momentum in biochemistry and (supramolecular) chemistry. However, the physicochemical origin of the exceptionally short (ca. 2.8 Å) oxygen-to-nucleobase plane distances observed in prototypical Z-DNA CpG steps remains unclear. High-level quantum mechanical calculations, including SAPT2+3 interaction energy decompositions, demonstrate that lp···π contacts do not result from n···π* orbital overlaps but from weak dispersion and electrostatic interactions combined with stereochemical effects imposed by the locally strained structural context. They also suggest that the carbon van der Waals (vdW) radii, originally derived for sp3 carbons, should not be used for smaller sp2 carbons attached to electron-withdrawing groups. Using a more adapted carbon vdW radius results in these lp···π contacts being no longer of the sub-vdW type. These findings challenge the whole lp···π concept that refers to elusive orbital interactions that fail to explain short interatomic contact distances.

CONFERENCES

26 – 28 February 2025: 1st Meeting of the Italian Scientific Community Working on Extrasolar Planets (Exoitaly), Rome, Italy
Title: "Formation of SO2 in exoplanets' atmospheres investigated by quantum chemistry"
Authors: <u>Klaudia Mráziková</u>, Franz Saija, Cesare Cecchi-Pestellini, Paul B. Rimmer, Martin Ferus, Giuseppe Cassone
Poster presentation
Role: presenter

26 June – 1 July 2023: 17th International Congress of Quantum Chemistry, Bratislava, Slovakia
Title: "QM investigation of phosphine synthesis in Venus' atmosphere"
Authors: <u>Klaudia Mráziková</u>, Martin Ferus, Giuseppe Cassone, Paul B. Rimmer, Antonín Knížek, Franz Saija, Homa Saeidfirozeh
Poster presentation
Role: presenter

18 – 22 July 2022: 2nd International Conference on Noncovalent Interactions, Strasbourg, France
Title: "Quantum chemistry reveals AMBER force field shortcomings for phosphate…π in nucleic acids"
Authors: <u>Klaudia Mráziková</u>, Pascal Auffinger, Holger Kruse, Vojtěch Mlýnský, Jiří Šponer

Poster presentation
Role: presenter

3 – 8 July 2022: WATOC 2020, Vancouver, Canada
Title: "Quantum chemistry reveals AMBER force field shortcomings for phosphate…π in nucleic acids"
Authors: Klaudia Mráziková, Pascal Auffinger, Holger Kruse, Vojtěch Mlýnský, Jiří Šponer
Poster presentation
Role: presenter

21 – 25 February 2022: Virtual Winter School on Computational Chemistry
Title: "Lone-pair…π contacts in nucleic acids: revision of Lennard-Jones parameters needed"
Authors: Klaudia Mráziková, Pascal Auffinger, Jiří Šponer, Holger Kruse
Single figure presentation
Role: presenter

25 May – 4 June 2021: 26th Annual Meeting of the RNA Society (RNA 2021) – online
Title: "Revealing short-range imbalances in AMBER force field for lone-pair…π contacts"
Authors: Klaudia Mráziková, Pascal Auffinger, Jiří Šponer, Vojtěch Mlýnský, Holger Kruse
Poster presentation
Role: presenter

25 – 26 June 2019: Joint Retreat 2019, Kouty, Czech Republic
Title: "Lone pair-π and anion-π interactions as stabilization factors of RNA tetraloops"
Authors: Klaudia Mráziková, Holger Kruse, Jiří Šponer, Pascal Auffinger
Oral presentation
Role: presenter

20 – 23 May 2019: XIXth Interdisciplinary Meeting of Young Life Scientists, Milovy, Czech Republic
Title: "Lone pair-π and anion-π interactions as stabilization factors of RNA tetraloops"
Authors: Klaudia Mráziková, Holger Kruse, Jiří Šponer, Pascal Auffinger
Oral presentation
Role: presenter

LECTURES

Seminar at the Faculty of Science of Masaryk University in Brno, Czech Republic
Title: "UUCG RNA tetraloop as a force-field challenge"
Event name: NCBR seminar (a course for doctoral and master students)
Date: 07/01/2021

INTERNSHIP ABROAD:

1 – 31 March 2022: Structure and Dynamics of Biomolecular Machines, Dr. Pascal Auffinger, University of Strasbourg, France

TEACHING EXPERIENCE:

Autumn 2020 and Autumn 2021: 5 lectures + exercises on Quantum Chemistry in a course Molecular modeling (MOMO) at the Department of Physical Chemistry of the Faculty of Science of Palacký University, Olomouc, Czech Republic

AWARDS:

The vice-rector's award for excellent results in doctoral studies, Masaryk University
Date: 19/10/2023

SKILLS

MOLECULAR MODELING:

QM and MD software: ORCA, TURBOMOLE, PSI4, Gaussian, Q-Chem, MOLPRO, CP2K, AMBER
Molecular builders/viewers: PyMOL, VMD, Avogadro, Molden, Jmol, IboView
Other tools: GNUplot, Grace (graphs); WebFR3D (bioinformatics); Inkscape, GIMP (graphics editors)

IT (all at user level):
Programming languages: Bash, Python, AWK
Computing skills: HPC computing
OS: Linux (Ubuntu), Windows
Other: LaTeX, Microsoft Office

LANGUAGES:
Slovak: native; **Czech**: fluent, **English**: proficient, **French**: basic, **Italian**: basic