Bernd Hartke

Aryl migration becoming more interesting with every step

Protecting groups are core features in the art of organic synthesis. Their utility drops when they start moving around. Recently, the Lindhorst group studied nitro-aryl migration at monosaccharides (Fig. 1), measuring the migration kinetics by NMR for four different sugars (mannose, galactose, glucose and altrose). They found migration speeds ranging from minutes to days, despite their prediction of a Meisenheimer intermediate as migration mechanism in all cases. Additionally, it was unclear if axial-axial cases (as in altrose) proceeded via a ring conformation inversion or via some different mechanism.

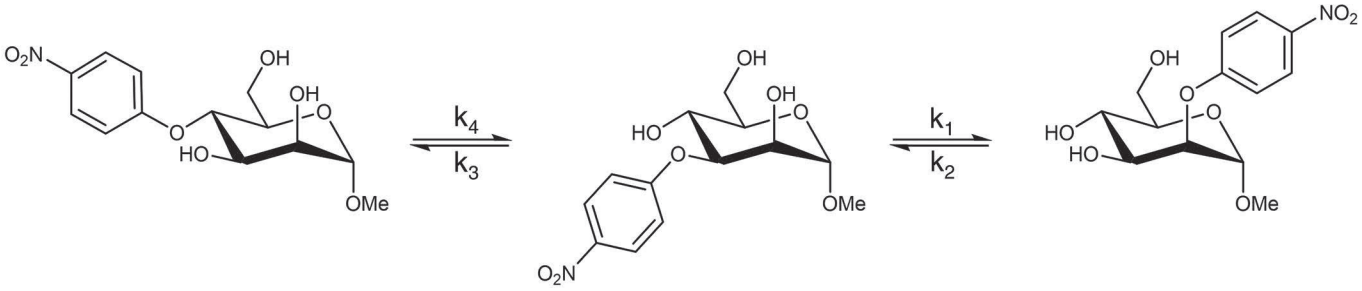


Fig. 1: Nitrophenyl migration at mannose, and the four relevant reaction rate constants.

My group was asked for theoretical support. We first extracted reaction rate constants from the measured kinetic data, by numerical solution of the kinetic differential equations with a self-written 4th-order Runge-Kutta integrator, combined with a derivative-free bound-constrained local optimization [1] to iteratively optimize initial rate constant guesses, minimizing the least-squares deviation between experimental and simulated kinetic data. Interestingly, the rate constant search space appeared to be unimodal and convex, since in almost all cases no multiple minima were obtained in repeated runs starting from very different initial guesses. Occasionally, too disparate rate constant values and insufficient experimental data for the slowly changing concentrations produced incomplete solutions. This could be fixed easily by employing balance equations: Since this is “closed-loop” kinetics, the total amount of reacting molecules stays the same and the total concentration changes always add up to zero. Note that this first theory task only needed two standard algorithms in numerical mathematics [2]. We are currently upgrading our chemistry curriculum at Kiel University, bringing basics of numerical mathematics in closer contact to our chemistry students, even if they specialize in organic or inorganic chemistry.

The second stage of our experiment-theory collaboration was investigation of the migration mechanisms. With nudged elastic band calculations and a few dedicated relaxed scans it was easy to establish that counter-migration of a proton or aryl migration to a full OH group is not possible energetically. Instead, the target OH group for the aryl migration needs to be deprotonated beforehand. This nicely explains the basic conditions needed in the experiment (MeONa in MeOH). However, for an anionic sugar-aryl moiety, the barrier for aryl migration was only 20-30 kJ/mol, while the experimental kinetic data (translated into effective activation energy barriers via the rate constants and Eyring’s transition-state theory equation) clearly indicated barriers on the order of 100 kJ/mol.

We did all the exploratory calculations at the r2scan-3c level of theory, with MeOH as continuum-model solvent. Test calculations confirmed the suspicion that this big difference between experiment and theory did not disappear at higher levels of theory, including double-hybrid functionals and CCSD(T). Instead, it turned out to be necessary to include the Na^+ cation into the calculations (together with an explicit solvent molecule): The negative charge of the reacting sugar-aryl system is fairly localized on the deprotonated OH group before and after migration, while in the Meisenheimer intermediate it is widely delocalized, covering both O-atoms and extending across the aryl ring to the nitro substituent in para position. This leads to strong stabilization of reactants and products via Coulomb interactions with Na^+, but only to a weak stabilization of the intermediate and of the transition states flanking it. This brings calculated overall barriers into the experimental range of about 100 kJ/mol. This

Prof. Dr. Bernd Hartke
Theoretische Chemie
Institut für Physikalische Chemie
Christian-Albrechts-Universität
Max-Eyth-Straße 2, D-24118 Kiel
hartke@pctc.uni-kiel.de
https://ravel.pctc.uni-kiel.de/

DOI-Nr.: 10.26125/95qr-ts83

surprising influence of the base cation could be confirmed by experiment: Going from MeONa to MeOK makes the migrations faster, simply because the K cation is larger than the Na cation, which makes its Coulomb interactions substantially weaker.

Our joint published paper [3] sells this as an interesting success story of a collaboration between theory and experiment, and the journal featured it with a cover illustration. However, the still ongoing "backstory", centrally including a BSc thesis by Mira Ihlow [4], is even more interesting, in several respects:

The paper covers only calculations for mannose. For altrose, preliminary results indicate that total ring inversion is feasible (its energy barrier is about 25 kJ/mol, which is much lower than the apparent migration barriers) but not necessary: Our reaction coordinates for ring inversion point to a two-step process, with two halves of the sugar ring inverting separately and successively, but only a half-inversion already places the involved OH groups into a relative position much more amenable to aryl migration. If aryl migration at altrose involves a full ring inversion or only half an inversion is still an open question.

The core system includes several rotatable single bonds, each featuring two or more rotamers that differ in energy by up to 20 kJ/mol, and this needs to be included in the reaction calculations, which we have not done to a sufficient extent so far. In particular, when the migrating aryl group moves from the Meisenheimer intermediate over to the target OH group, the reaction path branches into two possible rotamers for the final migration product, differing by 20 kJ/mol. This clearly influences the back-migration probability, if only from an energy perspective. Which influences operate decisively at this branch point is unexplored; I would not be surprised if actual dynamics were important here, which would necessitate an extensive trajectory study.

Our published reaction profile features a second barrier arising from cation counter-migration from the (deprotonated) target OH group to the (deprotonated) starting OH group (Fig. 2). This is an artifact. Mira calculated reaction profiles for an extended system, including 12-15 explicit MeOH molecules. There, this second barrier disappears, in favor of a continuous MeOH coordination of the cation -- but essentially without changes in the overall barrier heights.

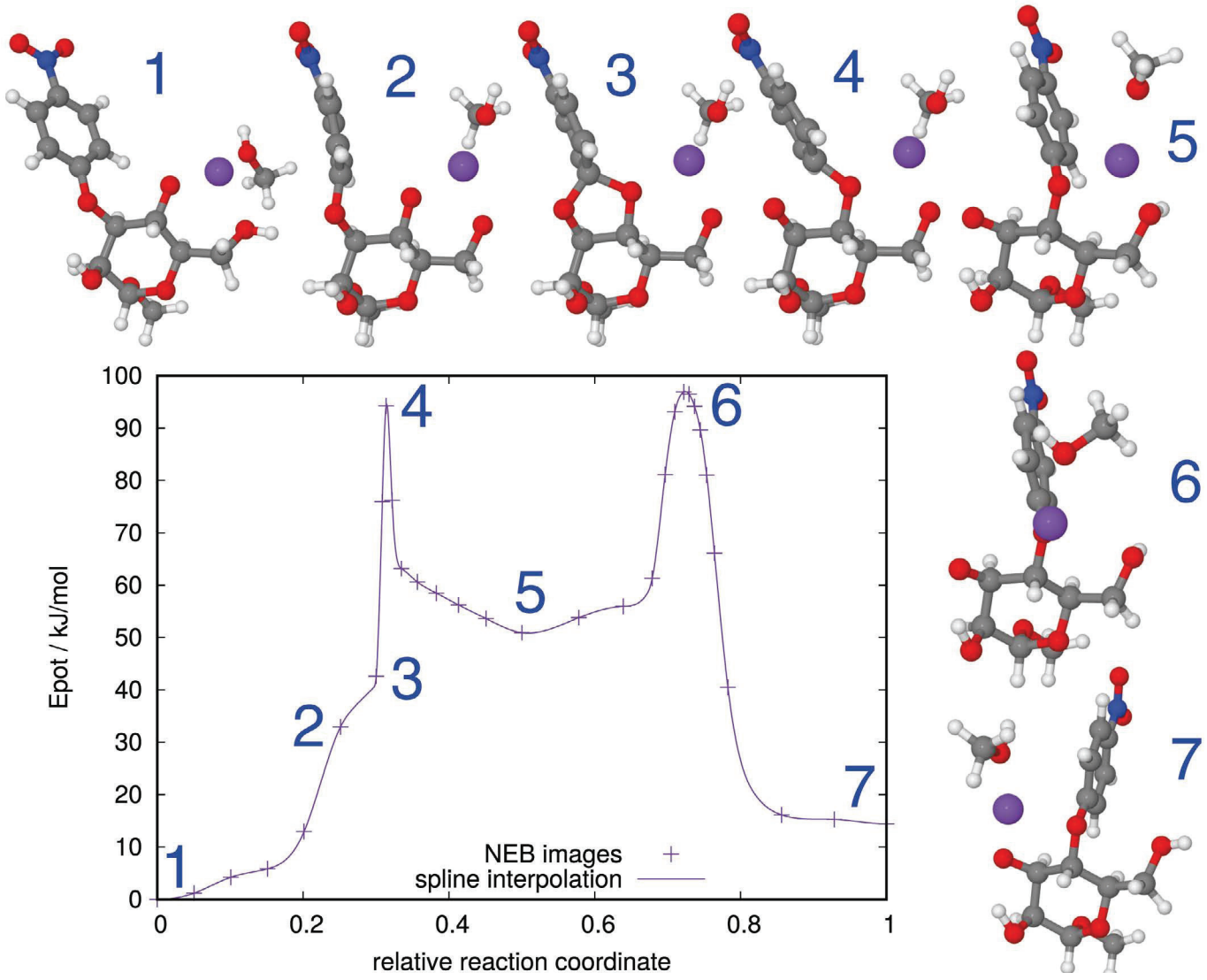


Fig. 2: Seven snapshots along the reaction coordinate of nitrophenyl migration at deprotonated mannose, with the Na cation and one explicit MeOH solvent molecule included, and the total electronic energy as a function of this reaction coordinate, calculated at the ωB2GP-PLYP/def2-TZVP level of theory, in a CP-CM-continuum model of MeOH as solvent.

Supported by decades of in-house experience with global optimization [5], we are sure to be able to find optimal explicit MeOH clusters around the reacting sugar-aryl system, but keeping this explicit solvent cluster optimal throughout the whole reaction turns out to be challenging. Joining optimal MeOH embeddings for reactants and products via the NEB algorithm either fails outright or produces clearly suboptimal clusters along the path. Locally optimizing the system from optimal clusters near the transition states down to reactants and products mostly works, but typically ends up with obviously non-optimal clusters at the reactants or products end. Sampling solvent configurations from a long molecular dynamics trajectory would be another option, but this will definitely result in MeOH configurations that are strongly suboptimal at the transition states. Last but not least, Mira found disturbingly many configurations on NEB-based reaction paths that could be relaxed back to reactants or products by local optimization, despite being separated from them by a substantial energy barrier along the path.

The ultimate aim of this collaboration was to explain all those disparate rate constants. However, all of the above effects modify energy profiles by 20-40 kJ/mol, which is larger than the span of the barriers inferred from experiment and larger than the expected errors of our low-end exploratory calculations. While we are confident to be able to resolve all these issues eventually, this collaboration between experiment and theory on an only seemingly simple system nicely illustrates not only that theory helps experiment to determine atomic-scale mechanisms but also that experiment helps theory to uncover gaps in theory toolboxes when applied to real-world problems.

Referenzen

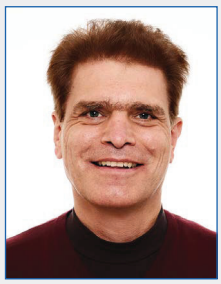
[1] Michael J. D. Powell: The BOBYQA algorithm for bound constrained optimization without derivatives, *Report No. DAMTP 2009/NA06,* Centre for Mathematical Sciences, University of Cambridge, UK 2009.

[2] William H. Press, Brian P. Flannery, Saul A. Teukolsky, William T. Vetterling: Numerical Recipes – The Art of Scientific Computing, *Cambridge University Press,* Cambridge 1990.

[3] Leon M. Friedrich, Clemens Lütjohann, Bernd Hartke, Thisbe K. Lindhorst: Migration of para-Nitrophenyl Groups in Methyl Pyranosides: Configuration and Conformation Determine the Kinetics, *Chem. Eur. J.* 2024 **30**, e202403117.

[4] Mira J. Ihlow: Je mehr, desto besser? Auswirkung von expliziten Lösungsmittelmolekülen auf die Arylwanderung an Zuckern, *BSc thesis,* Kiel University, 2024.

[5] Bernd Hartke: Global geometry optimization of clusters using Genetic Algorithms, *J. Phys. Chem.* 1993 **97**, 9973-9976.



Prof. Dr. Bernd Hartke

Bernd Hartke obtained his PhD in theoretical chemistry at the University of Würzburg, modeling nuclear motion in small molecules with quantum-mechanical wavepacket dynamics. During a two-year postdoc at UCLA, he coupled classical-mechanical nuclear trajectories with on-the-fly electronic structure theory at the generalized valence bond level, with applications to simulated annealing of small atomic clusters. After a brief stay at the University of Bielefeld, he completed his habilitation at the University of Stuttgart, with topics ranging from photochemistry simulations with wavepacket dynamics to global optimization of molecular clusters with evolutionary algorithms. Since 2002, he is professor for theoretical chemistry at Kiel University. While doing research on molecular motors, reactive force fields, catalysis by globally optimal electric fields and many other topics, he thoroughly enjoys frequent, diverse and productive collaboration projects with experimental colleagues.