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**Quantum Chemical Investigation of  
Molecules in External Electric Fields**

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**Dr. rer. nat.**

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**Revision notice**

This is a revised version created for publication. Compared to the original version, minor typing errors have been fixed on pages 1 and 10. Furthermore, some publications included in this dissertation are not displayed due to copyright reasons. The section “Acknowledgements” has been removed for privacy reasons.

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## Abstract

The use of oriented external electric fields (OEEFs) as a way to manipulate molecular bonds has recently gained popularity. Being a form of chemical catalysis, they can selectively change bond strengths and induce reactions. This has potential applications in mechanochemistry, a field that studies the application of mechanical force to selectively rupture bonds. This work investigates the accuracy of computational methods based on density functional theory (DFT) for calculating electronic structures in strong OEEFs. Through a broad benchmark study, the performance of various DFT methods for this application is quantified. Subsequently, the methodology is combined with a computational model applying mechanical force. The first ever computational investigation of the rupture behaviour of a mechanophore in an OEEF concludes that OEEFs can drastically alter the force required to rupture a mechanophore's scissile bond. Following that, a study of a mechanophore subjected to an OEEF in a simulated thermal environment shows that the effects that OEEFs have on the molecular structure are largely temperature-independent, even when mechanical force is applied.

## Zusammenfassung

Die Verwendung gerichteter externer elektrischer Felder (OEEFs) zur Beeinflussung chemischer Bindungen hat in den letzten Jahren deutlich an Bedeutung gewonnen. Als eine Art chemische Katalyse können OEEFs selektiv Bindungsstärken ändern und chemische Reaktionen herbeiführen. Besonders in der Mechanochemie, einem Feld, welches Moleküle unter mechanischer Spannung untersucht, ist dies von Interesse. Diese Arbeit untersucht die Genauigkeit von auf Dichtefunktionaltheorie (DFT) basierenden Methoden für die Berechnung von Molekülen in starken OEEFs. Über eine breit gefächerte Benchmark-Untersuchung wurde die Leistung verschiedener Dichtefunktionale bezüglich dieser Anwendung quantifiziert. Anschließend wurde die Methode um die Anwendung mechanischer Zugkraft erweitert. Erstmals wurde eine computergestützte Untersuchung des Bindungsbruchverhaltens von Mechanophoren in OEEFs durchgeführt. Sie konnte zeigen, dass ein OEEF die Kraft, die nötig ist, um in einem Mechanophor einen Bindungsbruch zu verursachen, drastisch verändern kann. Darauf aufbauend wurde ein Mechanophor in einer simulierten thermischen Umgebung einem OEEF ausgesetzt. Diese Simulation konnte zeigen, dass der Einfluss von OEEFs auf die Bindungsstruktur eines Moleküls nahezu temperaturunabhängig ist, auch, wenn das Molekül unter mechanischer Krafteinwirkung steht.

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# 1 Introduction

Oriented external electric fields (OEEFs) recently started to emerge as a major topic of importance in chemical research, particularly in the field of chemical catalysis.<sup>1,2</sup> They are capable of inducing chemical reactions by altering bond dissociation energies and stabilizing zwitterionic states, and can give control over chemical selectivity.<sup>1,3-6</sup> Selectively catalyzing a bond dissociation or chemical reaction requires precisely aligning the chemical bond relative to the OEEF. Achieving this experimentally is a major challenge as one needs to be able to know and precisely fixate a molecule's orientation. The seminal work by Aragonès *et al.*<sup>3</sup> in 2016 showed that it is possible to selectively control a Diels-Alder reaction using an OEEF experimentally, although it required a complex setup. Nevertheless, the breakthrough was followed by a growing interest in the field, resulting in an increasing number of computational investigations.<sup>3,5,7-9</sup>

The group I joined while working on this project, led by Prof. Dr. Tim Neudecker, specializes in mechanochemistry,<sup>10</sup> a field that investigates chemical reactions induced using mechanical stress. One branch of mechanochemistry is concerned with chemical reactions induced by tension, or mechanical pulling force. In polymer mechanochemistry, chemical reactions are induced by embedding molecules in polymer backbones and applying tension to them.<sup>11</sup> A notable example of this is the work by Davis *et al.*,<sup>12</sup> who embedded spiropyran in an elastomer backbone, causing the material's colour to shift as the material was pulled apart.<sup>13</sup> This ability to fixate the orientation of a force-sensitive molecule by embedding it in a polymer backbone inspired the idea of using strong electric fields to change the chemical reactivity of molecules under mechanical stress, with the hypothesis that OEEFs can be used to selectively alter the amount of force required to rupture a bond in a molecule. Combining OEEFs with mechanical force could not only allow greater control over the mechanical properties of molecules, it also would address the difficulty of aligning the molecule relative to the OEEF.

The primary objective of the work presented here is to, for the first time, investigate the effects that OEEFs have on molecules under mechanical stress, and the way that electric field effects and mechanical force interact with one another. I performed this investigation entirely *in silico*, using electronic structure methods based on density functional theory (DFT). As a first step, I found a need to determine the accuracy of such methods when calculating molecules in strong electric fields. Despite the growing number of computational investigations involving OEEFs, no such analysis had been done before. While DFT methods are known to work well with computational methods simulating mechanical stress on organic molecules,<sup>14</sup> it was not precisely known how accurately they describe organic molecules in strong electric fields. Therefore, the work presented in this dissertation is split into three distinct parts: In the first part, I conduct a benchmark study determining the accuracy of these methods. In the second part, I use the most suitable computational methodology found to perform investigations of model molecules under the simultaneous influence of an OEEF and mechanical stress. Lastly, I investigate a more realistic application scenario by performing simulations of a model molecule under mechanical stress in an OEEF at various different temperatures.

This dissertation is structured as follows: In Chapter 2, I provide background information broadly covering the major topics relevant for the presented research. In Chapter 3, I present the work I have done as part of this dissertation. As all research I conducted has been published in scientific literature, this chapter contains the three published research articles, each corresponding to one of the mentioned parts. In Chapter 4, I provide suggestions for potential research that may be done in the future to further the understanding of the interplay between OEEFs and mechanical force. Finally, in Appendix A, I briefly list all research projects unrelated to my dissertation that I participated in during the time I conducted my primary work.

## 2 Theoretical Background

### 2.1 Electronic Structure Methods

Methods for calculating the electronic structure of molecules generally fall into two categories: Those based on density functional theory (DFT) and those based on directly improving the Hartree-Fock (HF) energy, called post-Hartree-Fock (post-HF) methods. The following is meant to provide a brief overview of electronic structure methods relevant for this work.

#### 2.1.1 Post-Hartree-Fock Methods

This section is based on Chapters 3 and 4 in *Introduction to Computational Chemistry* by Frank Jensen.<sup>15</sup>

The Hartree-Fock method is a core component of modern electronic structure methods. By making the approximation that the wave function can be expressed using a single Slater determinant consisting of one-electron wave functions, it allows using the variational principle to solve the Schrödinger equation for larger molecules by minimizing the system's electronic energy. While this method allows accurately calculating up to 99% of the system's energy, HF only describes the important contribution of electron-electron correlation as an average interaction, putting the resulting energies outside of the realm of chemical accuracy.

There are a number of approaches for better describing electron-electron interactions to improve the HF energy. The most common practical approaches are based on perturbation theory or coupled-cluster (CC) theory. In perturbation theory, the HF Hamiltonian is considered as a base term  $\hat{H}^0$  that is "perturbed", or modified, by additional, independent operators  $\hat{H}'$  that result in the exact Hamiltonian  $\hat{H}$ . The strength of the perturbation is given by the variable parameter  $\lambda$ .

$$\hat{H} = \hat{H}^0 + \lambda\hat{H}' \quad (1)$$



The Møller-Plesset theory uses this to add the electron correlation energy that is missing in the Hartree-Fock method by separately calculating correction terms using excited Slater determinants. These terms originate from a Taylor expansion of the perturbation parameter  $\lambda$ , with higher-order terms including higher-order excitations. The sum of the zeroth-order term and the first-order term is equal to the HF energy, as including single excitations does not improve the Hartree-Fock wave function according to Brillouin's theorem. Therefore, MP theory only yields an improvement starting with the second-order term. The order of the method is defined by the order after which the Taylor expansion is truncated, making the Møller-Plesset 2 (MP2) method, which calculates the correction term for second excitations and adds them to the HF energy, the smallest MP method. For this, all double excitations from any two occupied orbitals  $i$  and  $j$  into any two unoccupied (virtual) orbitals  $a$  and  $b$  are calculated, using the corresponding orbitals  $\phi$  and orbital energies  $\epsilon$ .

$$E_{MP2} = E_{HF} + E^{(2)} \quad (2)$$

$$E^{(2)} = \sum_i^{\text{occ.}} \sum_{j>i}^{\text{occ.}} \sum_a^{\text{vir.}} \sum_{b>a}^{\text{vir.}} \frac{(\langle \phi_i \phi_j | \phi_a \phi_b \rangle - \langle \phi_i \phi_j | \phi_b \phi_a \rangle)^2}{\epsilon_i + \epsilon_j - \epsilon_a - \epsilon_b}$$

MP2 tends to overestimate the effect of electron correlation. Nevertheless, it provides significantly better results than HF at a reasonable computational cost, and is therefore a commonly used method for calculations of small and medium-sized molecules, particularly when combined with density functionals (see Section 2.1.2).

Another approach for improving on Hartree-Fock by including electron correlation as a correction term is coupled-cluster (CC) theory. Here, the exponential cluster operator  $\hat{T}$  is introduced, acting on the ground-state wave function  $\Phi_0$ .

$$\Psi \approx e^{\hat{T}} \Phi_0 \quad (3)$$

$\hat{T}$  describes all electronic excitations and mixes them into the wave function. It is separated into a sum of individual operators corresponding to the order of excitation, and the orders of excitation included in the calculations determines the order of the CC method.

$$\hat{T} = \hat{T}_1 + \hat{T}_2 + \hat{T}_3 + \dots \quad (4)$$

$e^{\hat{T}}$  is itself described through a Taylor expansion which, in practice, is also truncated. If only single and double excitations are considered, this leads to the term used in the Coupled-Cluster with Singles and Doubles (CCSD) method, resulting in an improved energy term.

$$e^{\hat{T}_1 + \hat{T}_2} = 1 + \hat{T}_1 + \left(\frac{1}{2}\hat{T}_1^2 + \hat{T}_2\right) + \left(\frac{1}{6}\hat{T}_1^3 + \hat{T}_2\hat{T}_1\right) + \left(\frac{1}{24}\hat{T}_1^4 + \frac{1}{2}\hat{T}_2\hat{T}_1 + \frac{1}{2}\hat{T}_2^2\right) + \dots \quad (5)$$

$$E_{CCSD} = \langle \Phi_0 | \hat{H} | e^{\hat{T}_1 + \hat{T}_2} \Phi_0 \rangle$$

One major advantage is that, despite CCSD only including  $\hat{T}_1$  and  $\hat{T}_2$ , excitations of higher order are implicitly described within  $e^{\hat{T}_1 + \hat{T}_2}$  as products of single and double excitations. This allows describing more correlation energy, making CCSD a very accurate electronic structure method.

Explicitly considering triple excitations in the coupled-cluster approach through  $\hat{T}_3$  is impractical for anything but the smallest molecules. However, the CCSD(T) method includes them by mixing coupled-cluster theory and perturbation theory: Single and double excitations are included in the cluster operator, while triple excitations are included as a perturbation on the system from MP theory. CCSD(T) is widely considered to be the “gold standard” of current electronic structure methods, generally providing the best results among all methods while being efficient enough to make the calculation of small and medium-sized molecules possible. It is for this reason that CCSD(T) is often used to generate reference values in benchmark studies, should accurate experimental data not be available.

## 2.1.2 Density Functional Methods

This section, unless cited otherwise, is based on Chapter 6 in *Introduction to Computational Chemistry* by Frank Jensen.<sup>15</sup>

Density functional theory (DFT) aims to solve the Schrödinger equation indirectly, calculating the energy through the system's electron density instead. This is done by introducing an energy functional  $E[\rho(r)]$ , which connects the electron density  $\rho$  to the system energy. In practice, the energy functional is defined following the Kohn-Sham theory.<sup>16</sup> The functional is split into a sum of multiple parts, each calculated separately. The kinetic energy assuming a non-interacting system  $E_{kin}$ , the nuclei-electron interaction energy  $E_{ne}$  that depends on the potential energy from nuclei  $V(r)$ , the coulomb energy between electrons  $E_{Coulomb}$ , and  $E_{XC}$ , the so-called exchange-correlation energy term.

$$\begin{aligned}
 E[\rho] &= E_{kin}[\rho] + E_{ne}[\rho] + E_{Coulomb}[\rho] + E_{XC}[\rho] \\
 E_{kin}[\rho] &= -\frac{1}{2}\nabla^2 \\
 E_{ne}[\rho] &= \int V(r)\rho(r)dr \\
 E_{Coulomb}[\rho] &= e^2 \int \frac{\rho(r')}{|r-r'|}dr' \\
 E_{XC}[\rho] &= ?
 \end{aligned} \tag{6}$$

All of these terms can be easily calculated analytically, except for  $E_{XC}$ , for which no solution is known.  $E_{XC}$  is a term containing non-trivial electron-electron interactions, specifically electron exchange energy and electron correlation energy. This functional is commonly separated further into the exchange term  $E_X$  and the correlation term  $E_C$ .

$$E_{XC}[\rho] = E_X[\rho] + E_C[\rho] \tag{7}$$

As the exact solution for these terms isn't known, a large number of models to approximate it have been developed over the past decades, trying to find a balance between accuracy and computational cost. These approximate functionals are commonly referred to simply as "density functionals". Some contain only exchange or correlation terms, while others include both directly. Density functionals are commonly categorized using what is known as *Jacob's Ladder*, where the "rungs" on the ladder correspond to the type of methods mixed in with the density functional, while the ascending order is associated with increased accuracy but also increasing computational cost.

The first rung on Jacob's Ladder corresponds to functionals using the local density approximation (LDA). While this approximation is still used in modern functionals, functionals based entirely on LDA only find niche uses in calculations of large periodic systems. Modern density functionals are based on the generalized gradient approximation (GGA). Pure GGA functionals correspond to rung 2 on Jacob's Ladder, while higher rungs are extensions of it. A GGA functional contains both the electron density and the gradient of the density in its equation. A meta-GGA (rung 3) would include the second derivative of the electron density, while hybrid GGAs and hybrid meta-GGAs (rung 4) are a linear combination of (meta-)GGA exchange and Hartree-Fock exchange. Finally, double hybrid (meta-)GGAs (rung 5) combine GGA exchange and correlation with Hartree-Fock exchange and MP2 correlation. The exact relationship between the electron densities and exchange energies, as well as ratios in which the energy is calculated from them is determined by a number of predefined constant parameters, the values of which are typically determined empirically. The number of parameters used, how they relate to one another and the electron density, and how their values are determined is what sets density functionals apart from one another, and finding better functionals and better parameters to more accurately represent quantum chemical effects is the core of density functional methodology research. On the other side, anyone utilizing DFT for electronic structure calculations needs to be aware of the differences between functionals, what advantages they have over one another, and which functional may fit their particular needs.

Modern density functional methods are often based on older ones, commonly being linear combinations of multiple methods. Separately developed exchange functionals and correlation functionals are combined this way, but in other cases, density functionals are developed with both exchange and correlation terms based on the same principles. This inheritance of principles and empirical terms makes it possible to attempt categorizing functionals into groups, ordered by the functionals they are based on rather than their rung on Jacob's Ladder. The following is meant to give a short overview over some common classes of density functionals, some of which are covered in the first part of this thesis (Chapter 3.1).

One of the largest groups of density functionals is based on the functionals developed by Becke. Becke's 88 (B88) exchange functional is a GGA exchange functional with only a single empirically fitted parameter.<sup>17</sup> It is only rarely used directly, but it is a part of a number of important derivatives. One such derivative is B3LYP,<sup>18,19</sup> a hybrid GGA which combines B88 with Hartree-Fock exchange and LYP,<sup>20</sup> a correlation term developed by Lee, Yang, and Parr. B3LYP is currently one of the most commonly used density functionals. B3LYP has further derivatives, often for special purposes, such as CAM-B3LYP,<sup>21</sup> a functional which contains long-range correction in its exchange term to correct non-local electron exchange, mixing in more HF exchange for long-range interactions (a so-called range-separated hybrid GGA). CAM-B3LYP is optimized for excited state calculations. A different derivative of B88 is B2PLYP,<sup>22</sup> a double hybrid GGA using B88 mixed with HF for exchange and LYP mixed with MP2 for correlation. Another exchange-correlation functional by Becke, B97,<sup>23</sup> has also spawned derivatives, specifically the  $\omega$ B97 group of functionals developed by Head-Gordon *et al.*<sup>24-29</sup> These are also range-separated hybrid GGAs, mixing in more HF exchange at longer distances.

One popular group of functionals is based on the very common PBE functional developed by Perdew, Burke, and Ernzerhof.<sup>30</sup> This exchange-correlation functional contains no empirically determined parameters, and all parameters are based on fundamental constants. As it contains equations for both exchange and correlation energy, it is directly mixed with other terms, such as in PBE0,<sup>31,32</sup> a hybrid functional combining PBE exchange with HF exchange, or DSD-PBEPBE,<sup>33</sup> a double-hybrid functional which additionally adds MP2 correlation and

several correction terms. There is a popular functional with no empirical parameters called TPSS,<sup>34</sup> a meta-GGA which also spawned derivatives such as TPSSh.<sup>35</sup>

In 2006, the group of Truhlar developed a larger group of combined exchange-correlation functionals termed “Minnesota functionals”. The most common ones are M06-L<sup>36</sup> (a meta-GGA) and M06-2X<sup>37</sup> (a hybrid meta-GGA). These are particularly common when calculating larger systems with significant non-covalent interactions. They are notable for having a large number of empirical parameters compared to most other groups of functionals – M06-L having 34 and M06-2X having 29.

Finally, a notable new exchange-correlation functional that is not directly based on previous ones is SCAN,<sup>38</sup> alongside its derivative r<sup>2</sup>SCAN,<sup>39</sup> which were published in 2015 and 2020, respectively. r<sup>2</sup>SCAN in particular has only been recently published, and as such there are not yet many benchmark studies including it in their testing. It has, however, received significant attention in a short period of time owing to the authors’ claims of high performance in both computational efficiency and accuracy.<sup>40</sup>

### 2.1.3 *Ab Initio* Molecular Dynamics

Electronic structure calculations typically solve the time-independent Schrödinger equation and calculate a molecule’s mean structure without considering temperature (“at 0 K”). To include the effects of temperature on a molecular structure in a calculation, one has to perform a simulation over time, as temperature at the molecular level represents the vibration of bonds and collisions between molecules, which both are time-dependent effects. Calculating molecular structures evolving over time is done using various molecular dynamics (MD) approaches. The most common type is classical MD, which calculates the kinetic strain energy acting on atoms using classical force fields from molecular mechanics to move atoms in space across discrete time steps.<sup>41</sup> Classical MD, while efficient and highly scalable, does not consider quantum mechanical effects and therefore does not provide accurate energies or bonding properties, particularly in bonding situations that classical mechanics cannot represent. Should one want to get accurate insights into those, the use of *ab initio* molecular

dynamics (AIMD) becomes necessary.<sup>42</sup> AIMD methods also move a molecule through time in discrete time steps, but calculate the electronic structure at each step to generate the equations of motion. The most widely used variant of AIMD is the Born-Oppenheimer molecular dynamics (BOMD) approach.<sup>42</sup> It follows the Born-Oppenheimer approximation, assuming that electrons will immediately follow any nuclear motion, and consequently only considers nuclear motion over time. At each time step, the time-independent Schrödinger equation is solved and the molecular structure is moved across the ground-state potential energy surface by calculating the forces acting on each atom according to its gradient. This allows using any electronic structure method for BOMD that can be used for single-point calculations. The effect of temperature is included by assigning initial nuclear velocities at the start of the simulation, usually using a Maxwell-Boltzmann distribution. The classical forces from these velocities are added to the internal forces calculated from the molecule's energy gradient. As initial nuclear velocities are assigned randomly, each simulation will have to be performed multiple times and for long time periods to be able to generate statistically significant means for molecular properties. Having to perform a single-point calculation each time step, BOMD simulations share the computational cost and scaling efficiency with geometry optimizations. Typical simulations use time steps of less than 0.5 fs, requiring thousands or tens of thousands of time steps to generate a trajectory on a meaningful time scale. BOMD simulations are typically performed using inexpensive DFT methods, but can still take weeks or months to complete on modern hardware.

## 2.2 Oriented External Electric Fields

### 2.2.1 Theory

This section is based on Section 10.1.1 in *Introduction to Computational Chemistry* by Frank Jensen.<sup>15</sup>

Oriented external electric fields (OEEFs) are linear electric fields applied along a specific orientation relative to the investigated material or molecule. As they are typically orders of magnitude larger than the molecule's internal electric field, they can be used to greatly alter molecular properties such as the geometry or stability. This allows using OEEFs for enabling chemical reactions that would be unfavourable under normal circumstances.

The electrostatic multipole expansion describing the interaction energy of a charge distribution with a field leads to the following equation.

$$E(r) = q\phi - \mu F - \frac{1}{2}Q \frac{\partial F}{\partial r} - \dots \quad (8)$$

For a molecule with charge  $q$  and potential  $\phi$ , dipole moment  $\mu$  and quadrupole moment  $Q$  in a field  $F$ . This series continues on to include higher-order expansion terms such as octapole moments, which are typically ignored in calculations.

For a homogenous OEEF, it is assumed that each part of the molecule experiences the same field and that the field strength is therefore uniform along its axis of orientation. Owing to this, an external field influences the molecule's dipole moment  $\mu$ , affecting the molecule's polarization. The dipole moment is itself described through a Taylor expansion of the electric field strength.

$$\mu(F) = \mu_0 + \alpha F + \frac{1}{2}\beta F^2 + \dots \quad (9)$$

$\mu_0$  is the molecule's permanent dipole,  $\alpha$  its polarizability,  $\beta$  its hyperpolarizability; this series, too, continues indefinitely.



If the interaction energy is treated as a perturbation on top of the field-free electronic energy, and assuming that the field is static, the total energy can itself be written as a Taylor series:

$$E(F) = E(0) + \frac{\partial E}{\partial F}F + \frac{1}{2} \frac{\partial^2 E}{\partial F^2}F^2 + \frac{1}{6} \frac{\partial^3 E}{\partial F^3}F^3 + \dots \quad (10)$$

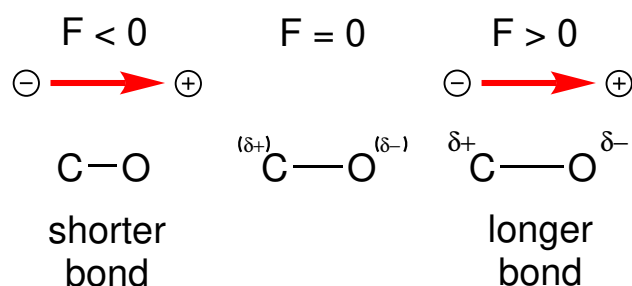
Inserting Equation 9 into Equation 10 directly yields the total energy based on the multipole properties.

$$E(F) = E(0) - \mu_0 F - \frac{1}{2} \alpha F^2 - \frac{1}{6} \beta F^3 + \dots \quad (11)$$

In electronic structure programs, the effect of an OEEF is applied to the electronic energy directly using the Taylor series expression. Typically, only  $\mu$  and  $\alpha$  are considered, and the series is cut off after the polarizability term.

## 2.2.2 Reactivity

Applying an OEEF has a variety of effects on a molecule. As electrons are drawn towards the positive pole of the electric field, it will increase the polarity along its axis. Molecules that would have no dipole moment without an applied electric field will gain an induced dipole moment (see Equation 9), and any molecular symmetry along the field axis will be broken. The shift of electrons towards the positive pole of the field leads to a shift in electron distribution, and a change in overlap between orbitals. Most commonly, it leads to a lengthening of bonds along the field axis compared to the field-less case (Figure 1). When the molecule's internal polarity is opposed to the field polarity, one can observe a shortening of the bond at low electric field strengths as the polarity is reduced and bond covalence increased. Applying a stronger field inverts the polarity, again leading to a lengthening of the bond. These effects can be strong enough to induce chemical reactions.<sup>1,2</sup>



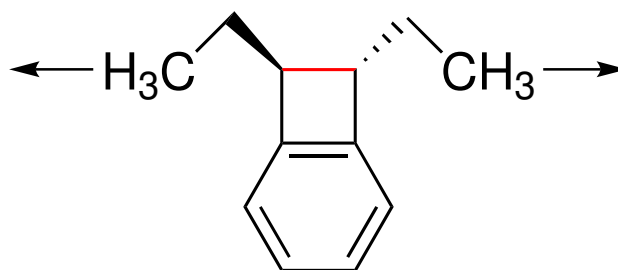
*Figure 1: External electric fields can shorten or lengthen molecular bonds depending on their orientation.*

## 2.3 Mechanochemistry

Mechanochemistry is the field of chemistry that focuses on studying the properties of molecules under mechanical stress.<sup>10</sup> Of particular interest is the activation of chemical reactions using mechanical action. The field is broad, covering any chemical reaction where mechanical force is involved. The forces that induce these chemical reactions are often macroscopic in nature, as is the case with ball-milling, ultrasound baths, or pulling. However, the effects that these forces have will be directly visible at the molecular level.

Mechanical forces in mechanochemistry can generally be separated into two categories: Directed and undirected. Undirected mechanical forces puts the individual molecules under pressure from all or random sides. This may occur in short bursts, like during ball-milling or in ultrasound baths, or over a long period of time, as is the case when placing a substance in a diamond anvil cell. The force may not always be a compressing force that shortens bonds and intermolecular distances, but it may also expand a molecule, as might be the case during an explosion. Contrary to this, directed mechanical force is consistently applied along a specific direction relative to the molecule's orientation. This can be achieved experimentally by orienting a single molecule with an atomic force probe and lifting the probe off the surface to apply stretching force, but it can also be achieved at a macroscopic level by creating linear polymer chains and then pulling on the ends of those chains.<sup>11,43,44</sup>

If a specific bond in a molecule is significantly weaker than any bonds in the polymer, mechanical force can be used to selectively rupture that particular bond. A substance that reacts to mechanical force in such a consistent way is known as a mechanophore.<sup>11,43,44</sup> Mechanophores are molecules that undergo consistent structural changes after a force-induced bond rupture (Figure 2). This typically occurs at forces in the range of a few nanonewtons.<sup>10</sup> When included in a polymer chain, a mechanophore forms an intentional weak point in the polymer structure where bond rupture will occur first. This allows adding novel properties to polymer materials. Examples for this include stress-induced colour changes<sup>11,12</sup> and the release of small molecules under strain.<sup>44-47</sup>



**Figure 2:** This benzocyclobutene derivative is an example for a simple mechanophore.<sup>48</sup> When sufficiently strong mechanical force is applied to the attached groups along the direction indicated by arrows, the scissile bond (shown in red) will selectively break.

Computationally subjecting molecules to mechanical stress allows determining changes in molecular properties with increasing force. For directed stretching force, an important part of determining the mechanical strength of a mechanophore is finding the minimum force required to break a bond, known as the rupture force. However, mechanical force is a macroscopic effect that isn't directly applicable on the molecular level, and therefore not trivial to include in electronic structure calculations. Over the years, a number of different approaches have been developed to address this.<sup>14,49</sup>

For directed stretching forces, two approaches for including mechanical force have emerged. The first and older method is known as COGEF ("constrained geometries simulate external force").<sup>50</sup> In COGEF, a geometry optimization is performed, during which the distance between two atoms in a molecule is constrained to a fixed value. The distance between these atoms may then be repeatedly increased and another optimization performed during each step. This allows building a potential energy curve along the stretching coordinate, mapping the distance between the two atoms being "pulled apart" to the electronic energy. The nuclear gradient of the electronic energy at the distorted geometry can then be used to determine the force required to achieve a given amount of stretching. As COGEF is based entirely on common constrained geometry optimizations, COGEF calculations can be performed using any quantum chemistry program package.

The second approach was published independently in the same year under two different names: FMPES (“force-modified potential energy surface”)<sup>51</sup> and EFEI (“external force is explicitly included”).<sup>52</sup> Both methods include an additional term in the electronic potential directly calculated from a stretching force applied between two atoms, and only differ in the origin points of the mechanical force; while EFEI is similar to COGEF in that it expects force to be applied along a stretching coordinate between two atoms, FMPES applies the force from arbitrary points in space.<sup>14</sup>

$$E(r) = E_0(r) + E_{Force}(r) \quad (12)$$

Because FMPES and EFEI add an additional term to the energy that is independent of other terms, they can be used with any electronic structure method, including AIMD simulations. During a geometry optimization, the additional potential from the applied mechanical force will cause bonds to lengthen, until eventually the internal restoring force of the stretched bonds becomes equal to the stretching force, resulting in an equilibrium geometry. If this does not occur, the bond ruptures. A direct connection between force and electronic structure allows more directly mapping external force to changes in molecular properties. Compared to COGEF, it also makes it easier to observe more complex structural changes occurring within a mechanophore that may alter the geometry in complex ways. Disadvantages compared to COGEF are that only few quantum chemistry programs implement EFEI or FMPES, and that it is often not possible to calculate geometries at forces higher than the rupture force, as the geometry will diverge past that point and no real minimum geometry can be found.

## 3 Publications

### 3.1 Research Article “Investigating the accuracy of density functional methods for molecules in electric fields”

**Scheele, T.;** Neudecker, T. Investigating the Accuracy of Density Functional Methods for Molecules in Electric Fields. *J. Chem. Phys.* **2023**, *159*, 124111, DOI: 10.1063/5.0164372

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The intent of the main research objective was to investigate the behaviour of molecules in OEEFs subjected to mechanical stress using model mechanophores. As a category of molecules that react strongly to mechanical stress, it was hypothesized that applying an OEEF to a mechanophore would show quantifiable effects. As the investigation of mechanophores in OEEFs was to be performed using DFT methods, I initially needed to choose a density functional method to perform the calculations with. However, there had not been any prior studies evaluating DFT methods in strong OEEFs, and there was no information on how accurate DFT methods are in these conditions. Because of this, the first project in this dissertation involves performing such a benchmark study. This only investigates the accuracy of DFT methods in OEEFs, with no involvement of mechanical force.

As a benchmark study needs reference data, and with no available experimental data, an accurate computational model needed to be chosen. For this purpose, the “gold standard” method CCSD(T) is used. The high computational cost of this method limits the size of the model systems that can be used for such a study. Therefore, mechanophores were not an option as model systems. Instead, a wide variety of small molecules, both inorganic and organic, is used to test a range of density functionals. The goal is to cover as many bonding situations as possible while keeping system sizes small enough to be able to calculate highly accurate reference data. This makes the resulting study a broad benchmark that generally validates DFT methods in strong electric fields.

The supporting information for this research article can be found in Appendix B.

Since its publication, this research article has been cited in scientific literature.<sup>54</sup>

## Abstract

The use of oriented external electric fields (OEEFs) as a potential tool for catalyzing chemical reactions has gained traction in recent years. Electronic structure calculations using OEEFs are commonly done using methods based on density functional theory (DFT), but until now, the performance of DFT methods for calculating molecules in OEEFs had not been assessed in a more general scope. Looking at the accuracy of molecular geometries, electronic energies, and electric dipole moments compared to accurate CCSD(T) data, we have investigated a wide variety of density functionals using different basis sets to determine how well the individual functionals perform on various types of chemical bonds. We found that most functionals accurately calculate geometries in OEEFs, and that small basis sets are sufficient in many cases. Calculations of electronic energies show a significant error introduced by the OEEF, which the use of a larger basis set helps mitigate. Our findings show that DFT methods can be used for accurate calculations in OEEFs, allowing researchers to make full use of the advantages that they bring.

## Scientific Contribution

I participated in the original conceptualization of this project. I developed the methodology together with Tim Neudecker. I chose the set of molecules used for the benchmark and the set of density functional methods and basis sets to investigate. I generated and performed all necessary calculations and validated, processed, and analyzed the resulting data. I created all visualizations found in the article. I wrote the additional software necessary for automatically performing the calculations, and for data processing, analysis, and visualization. As the lead author, I wrote the original manuscript of this research article and performed the edits requested during peer review.

**Scheele, T.**; Neudecker, T. Investigating the Accuracy of Density Functional Methods for Molecules in Electric Fields. *J. Chem. Phys.* **2023**, *159*, 124111, DOI: 10.1063/5.0164372

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### 3.2 Research Article “Using oriented external electric fields to manipulate rupture forces of mechanophores”

**Scheele, T.;** Neudecker, T. Using Oriented External Electric Fields to Manipulate Rupture Forces of Mechanophores. *Phys. Chem. Chem. Phys.* **2023**, *25*, 28070–28077, DOI: 10.1039/D3CP03965J

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Following the results of the benchmark study, it was now possible to use DFT methods for molecules in strong electric fields with full confidence in the accuracy of the methods. For this,  $\omega$ B97X-V was chosen as the method for all further calculations, since it showed good accuracy and a low dependence of the error on the electric field strength at a reasonable computational cost.

With a suitable computational method found, the second research project combines strong OEEFs with mechanical force in calculations. As an OEEF is a directional property, the type of mechanical force used for this investigation is also a directional one. The EFEI approach is used to apply directed pulling force along a stretching coordinate between two atoms. As the implementation of OEEFs and the implementation of EFEI both add independent additional terms to the electronic energy of the system, combining both was possible with no additional programming required. Despite that, this combination had not been investigated prior to this study.

Three model mechanophores covering a variety of bonding situations were investigated in electric fields of various strengths and orientations, with the goal of mapping changes in the rupture forces of the mechanophores as field strength and orientation relative to the stretching coordinate change. The study shows that EFEI and OEEF implementations can be combined to investigate the rupture forces of mechanophores in strong OEEFs. It also shows that OEEFs allow influencing molecular rupture forces in a very precise way by controlling the OEEFs strength and orientation, confirming the hypothesis that this work is based on.

Since its publication, this research article has been cited in scientific literature.<sup>56</sup>

## Abstract

Oriented External Electric Fields (OEEFs) can facilitate chemical reactions by selectively weakening bonds. This makes them a topic of interest in mechanochemistry, where mechanical force is used to rupture specific bonds in molecules. Using electronic structure calculations based on density functional theory (DFT), we investigate the effect of OEEFs on the mechanical force required to activate mechanophores. We demonstrate that OEEFs can greatly lower the rupture force of mechanophores, and that the degree of this effect highly depends on the angle relative to the mechanical force at which the field is being applied. The greatest lowering of the rupture force does not always occur at the point of perfect alignment between OEEF and the vector of mechanical force. Using natural bond orbital analysis, we show that mechanical force amplifies the effect that an OEEF has on the scissile bond of a mechanophore. By combining methods to simulate molecules in OEEFs with methods applying mechanical force, we present an effective tool for analyzing mechanophores in OEEFs and show that computationally determining optimal OEEFs for mechanophore activation can assist in the development of future experimental studies.

## Scientific Contribution

I participated in the original conceptualization of this project. I developed the methodology together with Tim Neudecker. I chose the molecules as well as the ranges of electric fields and mechanical force to investigate. I generated and performed all necessary calculations and validated, processed, and analyzed the resulting data. I created all visualizations found in the article. I wrote the additional software necessary for automatically performing the calculations, and for data processing, analysis, and visualization. Furthermore, I developed the necessary routine in the Q-Chem software package<sup>57</sup> that allows performing calculations with an electric field following a certain axis, which is available for use as of Q-Chem 6.2.0. As the lead author of this research article, I wrote the original manuscript and performed the edits requested during peer review.

**Scheele, T.;** Neudecker, T. Using Oriented External Electric Fields to Manipulate Rupture Forces of Mechanophores. *Phys. Chem. Chem. Phys.* **2023**, *25*, 28070–28077, DOI: 10.1039/D3CP03965J

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### 3.3 Research Article “On the Interplay Between Force, Temperature, and Electric Fields in the Rupture Process of Mechanophores”

**Scheele, T.;** Neudecker, T. On the Interplay Between Force, Temperature, and Electric Fields in the Rupture Process of Mechanophores. *ChemPhysChem* **2024**, e202400648, DOI: 10.1002/cphc.202400648  
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Directly building on the successful demonstration of computationally combining OEEFs and mechanical pulling force in the previous project, this project follows up by adding a third external effect in the form of temperature. In any realistic application scenario, thermal effects would be present, and there is a clear need to determine how temperature influences the previously demonstrated effect that OEEFs have on the scissile bond of a mechanophore.

Introducing thermal effects in a computational analysis is best performed using MD simulations. AIMD is based on quantum mechanical electronic structure calculations, which makes it the most suitable MD approach for this study. AIMD allows the use of the same methods for applying OEEFs and mechanical pulling force that were used in the previous projects, with the OEEF and EFEI approach being applied directly in the electronic structure calculation. The use of DFT methods enables highly accurate analysis of molecular properties such as bond lengths throughout the simulation, albeit at a great computational cost.

Using AIMD simulations, it is possible to combine the previously established methods for including OEEFs and mechanical pulling force in electronic structure calculations while also simulating a thermal environment. Here, rupture forces are not the focus of research, but instead mean bond lengths and bond vibration amplitudes of the model mechanophore's scissile bond. Various combinations of temperatures and electric field strengths are tested, both without and with applied mechanical pulling force. This allows analyzing the mean bond distance and vibration amplitudes of the mechanophore's scissile bond under different conditions. The study is the first computational demonstration of mechanical pulling force being applied to a mechanophore in an OEEF in an thermal environment. It shows that the previously shown effects of OEEFs on mechanophores under mechanical stress can also be found when temperature is present.

## Abstract

The use of oriented external electric fields (OEEFs) shows promise as an alternative approach to chemical catalysis. The ability to target a specific bond by aligning it with a bond-weakening electric field may be beneficial in mechanochemical reactions, which use mechanical force to selectively rupture bonds. Previous computational studies have focused on a static description of molecules in OEEFs, neglecting to test the influence of thermal oscillations on molecular stability. Here, we performed *ab initio* molecular dynamics (AIMD) simulations based on density functional theory (DFT) to investigate the behaviour of a model mechanophore under the simultaneous influence of thermal and electric field effects. We show that the change in bond length caused by a strong electric field is largely independent of the temperature, both without and with mechanical stretching forces applied to the molecule. The amplitude of thermal oscillations increases with increasing field strength and temperature, but at low temperatures, the application of mechanical force leads to an additional increase in amplitude. Our research shows that methods for applying mechanical force and OEEFs can be safely combined and included in an AIMD simulation at both low and high temperatures, allowing researchers to computationally investigate mechanochemical reactions in realistic application scenarios.

## Scientific Contribution

I conceptualized this project following the results of the previous one and acquired the necessary computational resources for it, which were granted at NHR@ZIB (formerly HLRN Berlin). I developed the methodology needed to perform repeated simulations across different temperatures, electric field strengths, and pulling forces. I generated and performed all necessary calculations and validated, processed, and analyzed the resulting data. I created all visualizations found in the article. I wrote the additional software necessary for automatically performing and concluding the simulations in an HPC environment, and for data processing, analysis, and visualization. As the lead author, I wrote the original manuscript of this research article and performed the edits requested during peer review.

# On the Interplay Between Force, Temperature, and Electric Fields in the Rupture Process of Mechanophores

Tarek Scheele<sup>[a]</sup> and Tim Neudecker<sup>\*[a, b, c]</sup>

The use of oriented external electric fields (OEEFs) shows promise as an alternative approach to chemical catalysis. The ability to target a specific bond by aligning it with a bond-weakening electric field may be beneficial in mechanochemical reactions, which use mechanical force to selectively rupture bonds. Previous computational studies have focused on a static description of molecules in OEEFs, neglecting to test the influence of thermal oscillations on molecular stability. Here, we performed *ab initio* molecular dynamics (AIMD) simulations based on density functional theory (DFT) to investigate the behaviour of a model mechanophore under the simultaneous influence of thermal and electric field effects. We show that the

change in bond length caused by a strong electric field is largely independent of the temperature, both without and with mechanical stretching forces applied to the molecule. The amplitude of thermal oscillations increases with increasing field strength and temperature, but at low temperatures, the application of mechanical force leads to an additional increase in amplitude. Our research shows that methods for applying mechanical force and OEEFs can be safely combined and included in an AIMD simulation at both low and high temperatures, allowing researchers to computationally investigate mechanochemical reactions in realistic application scenarios.

## Introduction

Oriented external electric fields (OEEFs) have established themselves as a focus of research into alternative forms of chemical catalysis.<sup>[1,2]</sup> By selectively stabilizing transition states that would be unfavourable under other conditions, OEEFs can enable unlikely reaction pathways.<sup>[3,4]</sup> In addition, the application of an OEEF allows for control over both reactivity and selectivity of various chemical reactions,<sup>[1,5–9]</sup> and, while far from straightforward experimentally, adjusting the strength and alignment of the OEEF with the molecule allows controlling the outcome of the reaction.<sup>[2,6,10]</sup>

While computational studies utilizing OEEFs have become increasingly common,<sup>[5–7,11–15]</sup> a newer field of interest for the potential applications of OEEFs is mechanochemistry,<sup>[16]</sup> particularly the reactivity of mechanophores. Mechanophores are molecules that react to mechanical stress.<sup>[17–19]</sup> They typically have a specific bond known as the scissile bond, which ruptures when enough mechanical force is applied, causing structural changes within the molecule. These changes can have various

effects, from changing the substance's colour<sup>[18,20]</sup> to releasing small molecules from the structure.<sup>[19,21–23]</sup> OEEFs and mechanical force are both capable of changing chemical properties,<sup>[24–27]</sup> sparking interest in studying the interaction between the two.

In a previous computational study,<sup>[28]</sup> we investigated the effects that the combination of OEEFs and mechanical force has on the structure of mechanophores. We found that the bond-weakening effects of these two external properties can amplify each other depending on their relative orientation. The investigation was done using relaxed ground state electronic structure calculations, but any practical application of this combined approach would also need to consider the system's temperature and its effect on the molecular geometry of a mechanophore. A computational study that considers the effect of temperature on a mechanophore would use molecular dynamics (MD) simulation methods to describe the evolution of the molecule's geometry over time. Specifically, the use of *ab initio* molecular dynamics (AIMD)<sup>[29]</sup> is a well-established option for investigating the behaviour and reactivity of mechanophores in a thermal environment.<sup>[30,31]</sup> In AIMD, the electronic structure of the system is calculated at each time step using electronic structure methods such as density functional theory (DFT).<sup>[32,33]</sup> While this enables the accurate description of the electronic changes caused by the application of mechanical force as well as OEEFs throughout the simulation,<sup>[30,34,35]</sup> no computational study exploring the influence of temperature on the behaviour of a strained mechanophore in an OEEF has been done until now.

In this work, we use a small model mechanophore to investigate how the influence of mechanical force and electric field on a scissile bond's geometry changes at different temperatures. Using AIMD simulations based on DFT, we explore the changes in the bond length as well as the thermally induced

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vibration of the mechanophore's scissile bond at different temperatures in static OEEFs. We compare the effects without and with mechanical stretching force applied along the molecule. Our goal in this work is to show how much the effects of OEEFs and mechanical force on a mechanophore's geometry change with the system's temperature, and how much the effects of temperature change with the OEEF. Additionally, we show that AIMD simulations can be used to combine the effects of OEEFs, mechanical force, and temperature to form a comprehensive model for investigating the behaviour of a mechanophore in a realistic application scenario.

The rest of this work is structured as follows: In Section "Computational Details", we present the methodology of our investigation and the computational methods we used for it. In Section "Results and Discussion", we discuss the behaviour of our model system at different temperatures and electric field strengths, both with and without mechanical force. Conclusions and outlook are given in Section "Conclusions and Outlook".

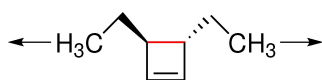
### Computational Details

For this work, we investigated a cyclobutene with minimal linkers (Figure 1). Cyclobutene derivatives are mechanophores with a scissile C–C bond that perform ring opening when mechanical force is applied.<sup>[36–38]</sup> The small size of the model structure allowed us to perform large-scale simulations.

Electronic structure calculations were performed using Q-Chem 6.1.1<sup>[39]</sup> at the  $\omega$ B97X-V/cc-pVDZ level of theory,<sup>[40,41]</sup> which has been shown to provide good accuracy when simulating organic molecules in strong electric fields.<sup>[42]</sup>

We investigated the influence of an OEEF on the scissile bond under thermal conditions. To achieve this, we performed single-molecule Born-Oppenheimer Molecular Dynamics (BOMD) simulations.<sup>[29]</sup> Each simulation calculated 11,000 time steps at 0.484 fs per time step, for 5.324 ps of total simulation time. The optimized starting geometry used for all simulations may be found in the supporting information. Simulations were performed at constant thermal energy by assigning initial atomic velocities using Maxwell-Boltzmann sampling. Simulations were performed at temperatures between 60 K and 600 K in steps of 60 K.

In this work, electric field strength is given in atomic units ( $1 \text{ a.u.} \approx 51.4 \text{ V \AA}^{-1}$ ). During the simulation, external electric fields between 0.00 a.u. and 0.05 a.u. in steps of 0.005 a.u. were applied along the stretching coordinate indicated by arrows in Figure 1. To apply the OEEF, we used a custom routine that always aligned the electric field with the marked atoms during the simulation. For each combination of simulation temperature and electric field strength, ten simulations were performed to obtain statistically significant results.



**Figure 1.** Schematic representation of the model mechanophore. The scissile bond is shown in red. The methyl groups to which mechanical forces are applied are indicated by arrows. The direction of the arrows coincides with the direction of the OEEF.

To investigate the effect that mechanical force has on the relationship between temperature and electric field, we performed the same set of simulations with the molecule experiencing a mechanical pulling force of 1 nN, applied using the External Force is Explicitly Included (EFEI) approach<sup>[43–45]</sup> as implemented in Q-Chem. The force was applied to the groups indicated by arrows in Figure 1.

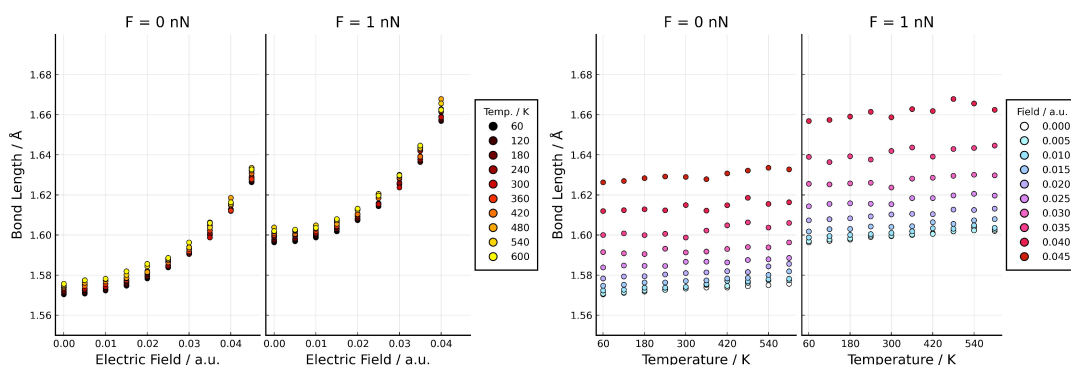
For each simulation, we tested whether bond rupture has occurred by measuring the length of the C–C bond. A video showing an example trajectory for such a rupture may be found in the supporting information. For each simulation that did not experience bond rupture, we calculated the mean bond length of the scissile bond along the simulation trajectory. To obtain the amplitude of the bond's vibration, we calculated the mean difference between the peak of each oscillation and the mean bond length. For each set of ten simulations with identical parameters, these values were averaged to obtain a given mean bond length and mean vibration amplitude.

### Results and Discussion

All molecules are stable across the simulation duration up to electric fields of 0.04 a.u. With no applied mechanical force, they are also stable in electric fields of 0.045 a.u. In stronger electric fields, the molecule experiences bond rupture along the scissile bond within a few C–C bond vibrations in every performed simulation. These results agree with previous observations showing that applying mechanical force to a molecule in an external electric field reduces its stability.<sup>[28]</sup> As this behaviour was observed regardless of the simulated temperature, we can additionally determine that the stability of the mechanophore's scissile bond in an electric field is independent of thermal conditions, up to temperatures where organic molecules decompose in real-world experiments regardless of any electric field, an effect which is not observable here owing to the short time span of the simulations.

Figure 2 shows the temperature-induced variation in the mean length of the scissile bond at different electric fields. While the mean C–C bond length increases continuously in stronger electric fields, we find that the magnitude of this increase is independent of the temperature of the system. The spread in mean bond length at different temperatures is small; looking at the change in bond length along the temperature axis shows no significant slope. Strong electric fields causing covalent bonds to lengthen is a well-known effect,<sup>[1]</sup> and this lengthening being independent of the temperature shows that effects of OEEFs on bond lengths observed in time-independent electronic structure calculations can be assumed to apply in thermal conditions as well, at least within the time frame considered in our simulations.

Applying mechanical force to the molecule during the simulation increases the overall length of the bond by between 0.02 Å and 0.04 Å compared to the length with no applied force. Applying mechanical force amplifies the lengthening of the bond with electric field strength. Without mechanical force, the scissile bond is on average 0.04 Å longer in an electric field of 0.04 a.u. compared to the bond length at no applied field. With applied mechanical force, this lengthening increases to



**Figure 2.** Mean bond length of the scissile bond of the model mechanophore for different electric fields at different simulation temperatures. The left and right hand side display the same data on different x axes. Each is shown without and with applied mechanical force of 1 nN.

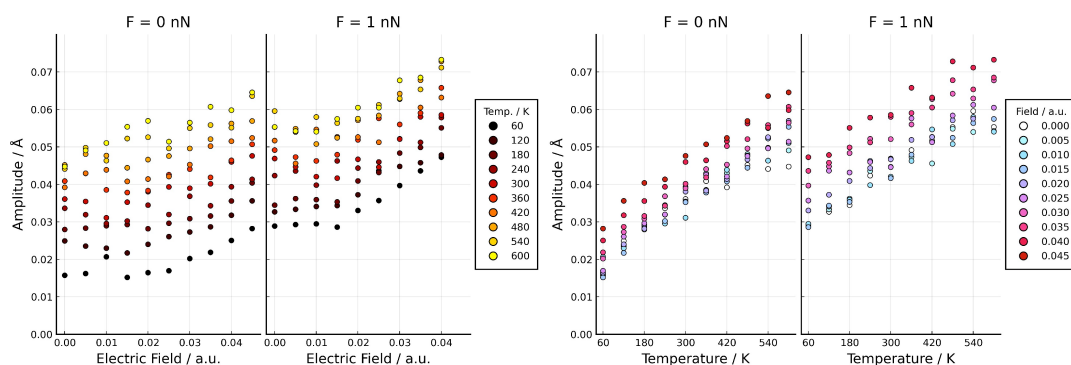
0.06 Å. This observation is in agreement with previous findings showing reduced rupture forces of mechanophores in strong electric fields.<sup>[28]</sup> This increase of the mechanophore's C–C bond length is also independent of the system temperature. Within the tested temperature range, no difference could be observed between low and high simulation temperatures.

The effect of electric field strength and temperature on the scissile bond's vibration amplitude can be found in Figure 3. Here, both the electric field and the temperature show an effect. The amplitude increases with increasing temperature as expected.

Notably, the amplitude also increases with increasing electric field strength. Though not continuous, there is a clear trend towards higher bond amplitudes in stronger electric fields. We expect that a larger sample size of oscillations for each data point, meaning significantly longer simulation times, would reveal a continuous increase. This increase, too, is in agreement with the observation that bonds generally weaken in strong electric fields. Weaker, longer bonds are more strongly affected by thermally induced atomic motion. This can be seen

by the amplitudes for different electric fields being more spread out at higher temperatures. At 60 K, the difference between the amplitude without an electric field and the amplitude at 0.04 a.u. is just over 0.01 Å, while at 600 K, it is close to 0.02 Å.

Applying mechanical force significantly increases the vibration amplitude at low temperatures, but has a much smaller effect at higher temperatures. The amplitudes do not differ significantly between the simulations with and without force at high temperatures. This leads to amplitudes overall being closer to the high-temperature values. This behaviour has not been previously reported in literature. We hypothesize that at low temperatures, the stretching of the molecule increases the effect that the thermal energy has on the atomic motion of the central carbon atoms by increasing the distance between the central carbon atoms and the other carbon atoms along the stretching coordinate, giving the central atoms more space to vibrate. At high temperatures, this effect is no longer relevant as the atoms have enough thermal energy to reach the same vibration amplitudes without mechanical force.



**Figure 3.** Mean bond vibration amplitude of the scissile bond of the model mechanophore for different electric field strengths at different simulation temperatures. The left and right hand side display the same data on different x axes. Each is shown without and with applied mechanical force of 1 nN.



The effect appears to be independent of the electric field strength. The trend of stronger electric fields causing increased vibration amplitudes is also observed when mechanical force is applied, but the higher spread at high temperatures can no longer be observed. Low temperatures also show a higher spread here, as weakening the bond through the application of mechanical force complements the weakening caused by the OEEF, as discussed previously.<sup>[28]</sup>

## Conclusions and Outlook

To summarize, we used AIMD simulations of a model mechanophore in an OEEF at different system temperatures to investigate the effect that thermal oscillations and an electric field have on the scissile bond when combined, with and without the additional influence of mechanical pulling force applied to the mechanophore. We found that the bond lengthening caused by the electric field is largely independent of the system temperature. The increase in bond length when mechanical force is applied also does not change with increasing temperature. The bond vibration amplitude changes both with increasing electric field strength and increasing temperature. Applying mechanical force significantly increases the vibration amplitude at low temperatures, but not at high temperatures.

We conclude that investigations of a mechanophore's scissile bond using AIMD simulations can safely be performed in strong electric fields at various temperatures. This is of particular interest for the application of mechanical force to mechanophores in an electric field while considering the realistic thermal vibrations of molecules. As the time span covered by our simulations is short, it is possible that there are dynamical effects that were not observed in this work. A future investigation using simulation methods with lower computational cost would be of interest here, though care must be taken that they are able to correctly describe the effects of mechanical force and electric fields on the mechanophore's electronic structure. On the time scale used in AIMD simulations, this is of no concern, enabling future research into mechanically induced reactions in electric and thermal environments.

## Acknowledgements

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## Conflict of Interests

The authors declare no conflicts of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Keywords:** Oriented External Electric Fields · Mechanochemistry · Density functional theory · ab initio molecular dynamics

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## 4 Conclusions and Outlook

The work presented in this dissertation opens up the field of computational investigations of molecular bonds in external electric fields. In the first part, I established DFT as a reliable electronic structure method for calculating molecules in strong electric fields. I tested various density functionals for their accuracy in these conditions, comparing geometries and energies calculated with them to accurate reference data. The work provides insight into the behaviour of DFT methods in strong electric fields, and the conditions under which they may be used while maintaining chemical accuracy. It is a valuable resource for other researchers doing electronic structure calculations in OEEFs, serving as a guide when choosing a DFT method suitable for their research.

In the second part, I investigated the effects that OEEFs and mechanical stretching force have on mechanophores when combined. For the first time, mechanophores have been computationally subjected to mechanical stress inside a strong OEEF. The results demonstrate that OEEFs can be used to selectively change the rupture forces of mechanophores by adjusting the strength and orientation of the electric field relative to the stretching coordinate. However, the study was limited by the small number of model mechanophores that were used for the investigation. Should these effects be studied for a larger number of mechanophores of different types in the future, it would provide much greater insight into how exactly the two effects amplify one another. Of particular interest would be a study on how rupture forces change with other types of scissile bonds that were not covered by this work, and to eventually establish a deeper understanding of the relationship between the rupture behaviour in OEEFs and the strength and polarity of a bond.

The third part of this work investigates the effects of electric fields on a model mechanophore in a more realistic application scenario by introducing a thermal environment. For this, AIMD simulations were used to inspect a mechanophore's thermal vibrations while in a strong OEEF at various temperatures. The discovery that temperature does not significantly affect the influence of OEEFs on the scissile bond of a mechanophore, even under mechanical stress,

means that future investigations of molecules under mechanical stress in OEEFs can safely be performed using AIMD simulations.

Having established that the combination of mechanical force and OEEFs has a great effect on mechanophores, a natural next step will be investigating a mechanochemical reaction under such conditions. Determining reaction coordinates in different fields using different stretching forces would give insight into how much a mechanochemical reaction may be fine-tuned by applying an OEEF during the reaction. Here, both the direction and the intensity of the field will be interesting to investigate with different types of reactions using both symmetric and asymmetric mechanophores. The symmetry-breaking effect of electric fields could lead to transition states that aren't normally seen in mechanochemical reactions.

After demonstrating that the effect of temperature on the OEEF-force interaction is minimal, a major next step following up on the third project would be investigating reaction kinetics in a thermal environment by performing further AIMD simulations. This would have to be done for a very small model reaction due to the high computational cost. While less expensive simulation methods are presently not capable of accurately describing both effects at the same time, it would nonetheless be a major step towards deepening our understanding of the ways in which OEEFs can be used to catalyze mechanochemical reactions.

## A Other Research

Throughout the duration of my primary research project, I was involved as a collaborator in a number of other projects. The following chapter lists the published research articles that came from those projects and details my contributions to them.

### A.1 Research Article “Software for the frontiers of quantum chemistry: An overview of developments in the Q-Chem 5 package”

Epifanovsky, E.; Gilbert, A. T. B.; Feng, X.; Lee, J.; Mao, Y.; Mardirossian, N.; Pokhilko, P.; White, A. F.; Coons, M. P.; Dempwolff, A. L.; Gan, Z.; Hait, D.; Horn, P. R.; Jacobson, L. D.; Kaliman, I.; Kussmann, J.; Lange, A. W.; Lao, K. U.; Levine, D. S.; Liu, J.; McKenzie, S. C.; Morrison, A. F.; Nanda, K. D.; Plasser, F.; Rehn, D. R.; Vidal, M. L.; You, Z.-Q.; Zhu, Y.; Alam, B.; Albrecht, B. J.; Aldossary, A.; Alguire, E.; Andersen, J. H.; Athavale, V.; Barton, D.; Begam, K.; Behn, A.; Bellonzi, N.; Bernard, Y. A.; Berquist, E. J.; Burton, H. G. A.; Carreras, A.; Carter-Fenk, K.; Chakraborty, R.; Chien, A. D.; Closser, K. D.; Cofer-Shabica, V.; Dasgupta, S.; de Wergifosse, M.; Deng, J.; Diedenhofen, M.; Do, H.; Ehlert, S.; Fang, P.-T.; Fatehi, S.; Feng, Q.; Friedhoff, T.; Gayvert, J.; Ge, Q.; Gidofalvi, G.; Goldey, M.; Gomes, J.; González-Espinoza, C. E.; Gulania, S.; Gunina, A. O.; Hanson-Heine, M. W. D.; Harbach, P. H. P.; Hauser, A.; Herbst, M. F.; Hernández Vera, M.; Hodecker, M.; Holden, Z. C.; Houck, S.; Huang, X.; Hui, K.; Huynh, B. C.; Ivanov, M.; Jász, Á.; Ji, H.; Jiang, H.; Kaduk, B.; Kähler, S.; Khistyayev, K.; Kim, J.; Kis, G.; Klunzinger, P.; Koczor-Benda, Z.; Koh, J. H.; Kosenkov, D.; Koulias, L.; Kowalczyk, T.; Krauter, C. M.; Kue, K.; Kunitsa, A.; Kus, T.; Ladjanski, I.; Landau, A.; Lawler, K. V.; Lefrancois, D.; Lehtola, S.; Li, R. R.; Li, Y.-P.; Liang, J.; Liebenthal, M.; Lin, H.-H.; Lin, Y.-S.; Liu, F.; Liu, K.-Y.; Loipersberger, M.; Luenser, A.; Manjanath, A.; Manohar, P.; Mansoor, E.; Manzer, S. F.; Mao, S.-P.; Marenich, A. V.; Markovich, T.; Mason, S.; Maurer, S. A.; McLaughlin, P. F.; Menger, M. F. S. J.; Mewes, J.-M.; Mewes, S. A.; Morgante, P.; Mullinax, J. W.; Oosterbaan, K. J.; Paran, G.; Paul, A. C.; Paul, S. K.; Pavošević, F.; Pei, Z.; Prager, S.; Proynov, E. I.; Rák, Á.; Ramos-Cordoba, E.; Rana, B.; Rask, A. E.; Rettig, A.; Richard, R. M.; Rob, F.; Rossomme, E.; **Scheele, T.**; Scheurer, M.; Schneider, M.; Sergueev, N.; Sharada, S. M.; Skomorowski, W.; Small, D. W.; Stein, C. J.; Su, Y.-C.; Sundstrom, E. J.; Tao, Z.; Thirman, J.; Tornai, G. J.; Tsuchimochi, T.; Tubman, N. M.; Veccham, S. P.; Vydrov, O.; Wenzel, J.; Witte, J.; Yamada, A.; Yao, K.; Yeganeh, S.; Yost, S. R.; Zech, A.; Zhang, I. Y.; Zhang, X.; Zhang, Y.; Zuev, D.; Aspuru-Guzik, A.; Bell, A. T.; Besley, N. A.; Bravaya, K. B.; Brooks, B. R.; Casanova, D.; Chai, J.-D.; Coriani, S.; Cramer, C. J.; Cserey, G.; DePrince, A. E.; DiStasio, R. A.; Dreuw, A.; Dunietz, B. D.; Furlani, T. R.; Goddard, W. A.; Hammes-Schiffer, S.; Head-Gordon, T.; Hehre, W. J.; Hsu, C.-P.; Jagau, T.-C.; Jung, Y.; Klamt, A.; Kong, J.; Lambrecht, D. S.; Liang, W.; Mayhall, N. J.; McCurdy, C. W.; Neaton, J. B.; Ochsenfeld, C.; Parkhill, J. A.; Peverati, R.; Rassolov, V. A.; Shao, Y.; Slipchenko, L. V.; Stauch, T.; Steele, R. P.; Subotnik, J. E.; Thom, A. J. W.; Tkatchenko, A.; Truhlar, D. G.; Van Voorhis, T.; Wesolowski, T. A.; Whaley, K. B.; Woodcock, H. L.; Zimmerman, P. M.; Faraji, S.; Gill, P. M. W.; Head-Gordon, M.; Herbert, J. M.; Krylov, A. I. Software for the Frontiers of Quantum Chemistry: An Overview of Developments in the Q-Chem 5 Package. *J. Chem. Phys.* **2021**, *155*, 084801, DOI: 10.1063/5.0055522

## Abstract

This article summarizes technical advances contained in the fifth major release of the Q-Chem quantum chemistry program package, covering developments since 2015. A comprehensive library of exchange–correlation functionals, along with a suite of correlated many-body methods, continues to be a hallmark of the Q-Chem software. The many-body methods include novel variants of both coupled-cluster and configuration-interaction approaches along with methods based on the algebraic diagrammatic construction and variational reduced density-matrix methods. Methods highlighted in Q-Chem 5 include a suite of tools for modeling core-level spectroscopy, methods for describing metastable resonances, methods for computing vibronic spectra, the nuclear–electronic orbital method, and several different energy decomposition analysis techniques. High-performance capabilities including multithreaded parallelism and support for calculations on graphics processing units are described. Q-Chem boasts a community of well over 100 active academic developers, and the continuing evolution of the software is supported by an “open teamware” model and an increasingly modular design.

## Scientific Contribution

As part of my work investigating the effect of mechanical force on molecules in OEEFs, I used the Q-Chem software to apply mechanical force and electric fields at the same time. At the start of the project, the Q-Chem software only allowed applying an OEEF in a static direction that could not change throughout a calculation. In order to more realistically model an oriented mechanophore, I implemented a custom routine that allowed the OEEF to follow the coordinates of two atoms; the field would be oriented to run parallel to the line drawn by the atoms, similarly to EFEI. This ensured that the mechanical stretching coordinate and the direction of the OEEF were always perfectly aligned. This custom routine is now available for use in Q-Chem.

## A.2 Research Article “Alliacane-Type Secondary Metabolites from Submerged Cultures of the Basidiomycete *Clitocybe nebularis*”

Schrey, H.; Scheele, T.; Ulonska, C.; Nedder, D. L.; Neudecker, T.; Spiteller, P.; Stadler, M. Alliacane-Type Secondary Metabolites from Submerged Cultures of the Basidiomycete *Clitocybe Nebularis*. *J. Nat. Prod.* **2022**, *85*, 2363–2371, DOI: 10.1021/acs.jnatprod.2c00554

### Abstract

Seven sesquiterpenoids, named nebucanes A–G (1–7), featuring a rare alliacane scaffold with unprecedented furan or pyrrole functions, were isolated from the fermentation broth of *Clitocybe nebularis*. Their structures were established on the basis of 1D/2D NMR spectroscopic analyses, HR-(+)-ESIMS spectra, and comparison of measured and calculated CD spectra for determination of the absolute configuration. Assessing the biological activities, nebucane D (4) exhibited antifungal effects against *Rhodotorula glutinis*, while nebucane G (7) displayed significant cytotoxicity against MCF-7 and A431 cell lines.

### Scientific Contribution

In this work, seven secondary metabolites of *Clitocybe nebularis* were isolated and analyzed. As part of the structure elucidation, I performed computational geometry optimizations of the compounds. I calculated and visualized electronic circular dichroism (ECD) spectra of potential absolute configurations and compared them to experimental ECD spectra. The resulting spectra allowed determining the absolute configurations of the substances.

### A.3 Research Article “Can a Finite Chain of Hydrogen Cyanide Molecules Model a Crystal?”

Hsieh, C.-M.; Grabbet, B.; Zeller, F.; Benter, S.; **Scheele, T.**; Sieroka, N.; Neudecker, T. Can a Finite Chain of Hydrogen Cyanide Molecules Model a Crystal? *ChemPhysChem* **2022**, *23*, e202200414, DOI: 10.1002/cphc.202200414

#### Abstract

When calculating structural or spectroscopic properties of molecular crystals, the question arises whether it is sufficient to simulate only a single molecule or a small molecular cluster or whether the simulation of the entire crystal is indispensable. In this work we juxtapose calculations on the high-pressure structural properties of the (periodic) HCN crystal and chains of HCN molecules of finite length. We find that, in most cases, the behavior of the crystal can be reproduced by computational methods simulating only around 15 molecules. The pressure-induced lengthening of the C—H bond in HCN found in calculations on both the periodic and finite material are explained in terms of orbital interaction. Our results pave the way for a more thorough understanding of high-pressure structural properties of materials and give incentives for the design of materials that expand under pressure. In addition, they shed light on the complementarity between calculations on periodic materials and systems of finite size.

#### Scientific Contribution

In this work, chains of HCN molecules were computationally investigated under high pressure to investigate bulk properties emerging in longer chains. Here, I performed calculations of natural bond orbitals (NBOs)<sup>61</sup> for chains of different lengths and analyzed orbital interactions to explain differences in interatomic distances that were observed in the calculations.



## A.4 Research Article “Synthesis and crystal structure of 2-(anthracen-9-yl)-1-(*tert*-butyldimethylsilyl)-3,6-dihydro-1 $\lambda^4$ ,2 $\lambda^4$ -azaborinine”

Gliese, P. J.; Appiarius, Y.; Scheele, T.; Lork, E.; Neudecker, T.; Staubitz, A. Synthesis and Crystal Structure of 2-(Anthracen-9-Yl)-1-(Tert-Butyldimethylsilyl)-3,6-Dihydro-1 $\lambda^4$ ,2 $\lambda^4$ -Azaborinine. *Acta Cryst E* **2023**, *79*, DOI: 10.1107/S2056989023008381

### Abstract

The title compound, C<sub>24</sub>H<sub>30</sub>BNSi (I), is an asymmetric 1,2,3,6-tetrahydro-1,2-azaborinine consisting of a BN-substituted cyclohexadiene analog with a *B*-anthracenyl substituent. A ring-closing metathesis with subsequent substitution of the obtained BCl 1,2-azaborinine using anthracenyl lithium yielded the title compound I. The asymmetric unit ( $Z = 8$ ) belongs to the orthorhombic space group *Pbca* and shows an elongated N—C bond compared to previously reported BN-1,4-cyclohexadiene [Abbey *et al.* (2008) *J. Am. Chem. Soc.* **130**, 7250–7252]. The primarily contributing surface interactions are H $\cdots$ H and C $\cdots$ H/H $\cdots$ C (as elucidated by Hirshfeld surface analysis) which are dominated by van der Waals forces. Moreover, the non-aromatic BN heterocycle and the protecting group exhibit intra- and intermolecular C–H $\cdots$  $\pi$  interactions, respectively, with the anthracenyl substituent.

### Scientific Contribution

This work details the synthesis and structure of a novel azaborinine compound. For this work, I performed a computational geometry optimization of the compound followed by an NBO analysis. From the NBOs, I further performed a natural population analysis (NPA) of calculated natural localized molecular orbitals (NLMOs) to obtain bond orders.<sup>61</sup> Using these bond orders, I analyzed the intramolecular interactions within the ring of the compound. As part of this project, I calculated NBOs and bond orders this way for a total of nine different compounds; only one of these compounds has been published as of now.

## A.5 Submitted Manuscript “Chiral Triazole-substituted Iodonium Salts in Enantioselective Halogen Bond Catalysis”

Damrath, M.; Scheele, T.; Duvinage, D.; Neudecker, T.; Nachtsheim, B. J. Chiral Triazole-substituted Iodonium Salts in Enantioselective Halogen Bond Catalysis. *ChemRxiv* 2024, DOI: 10.26434/chemrxiv-2024-kkrjl

### Abstract

Herein, we present the synthesis of chiral triazole-based diaryliodonium salts and their application as monodentate asymmetric iodine(III) derivatives in halogen bond (XB) catalyzed reactions. These potential Lewis acids were successfully benchmarked in the vinylogous Mannich reaction of cyanomethyl coumarin with isatin-derived ketimine to obtain the addition product in up to 99% yield and >99:1 e.r. Furthermore, these halogen bond catalysts allowed an efficient functionalization of ketimines with various alcohols toward N,O-acetals in up to 99% yield and 90:10 e.r. Additionally, we studied the origin of the enantioselectivity based on Density Functional Theory (DFT) and the catalyst crystal structure. These unveiled the first approach of asymmetric induction facilitated by using  $\sigma$ -hole stabilized chiral moieties in iodine(III)-based catalysts and exclusively predicated upon XB activation.

### Scientific Contribution

This work presents a group of novel diaryliodonium salts that perform efficiently and selectively in halogen bond catalyzed reactions. For this project, I performed geometry optimizations of individual reagents and catalysts as well as the catalyst-reagent complexes and calculated complexation energies. I assisted in the analysis of the complexation energies and intermolecular interactions to determine the most likely orientations of the reagent in the complex.

## B Supporting Information

### B.1 Supporting Information “Investigating the accuracy of density functional methods for molecules in electric fields”

**Scheele, T.**; Neudecker, T. Investigating the Accuracy of Density Functional Methods for Molecules in Electric Fields. *J. Chem. Phys.* **2023**, *159*, 124111, DOI: 10.1063/5.0164372

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## C References

References used for previously unpublished parts of this dissertation are found here. Each published research article has its references listed separately at the end of the article.

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