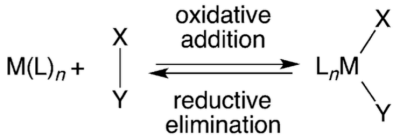
Exercise 4. Palladium-Catalyzed Bond Activation

Reading material

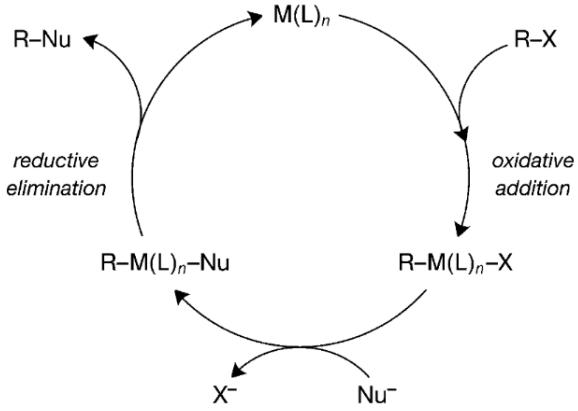
A. Diefenbach, F. M. Bickelhaupt, *J. Phys. Chem. A* 2004, *5*, *108*, 8460–8466.
W.-J. van Zeist, R. Visser, F. M. Bickelhaupt, *Chem. Eur. J.* 2009, *15*, 6112–6115.
L. P. Wolters, W.-J. van Zeist, F. M. Bickelhaupt, *Chem. Eur. J.* 2014, *20*, 11370–11381.
P. Vermeeren, X. Sun, F. M. Bickelhaupt, *Sci. Rep.* 2018, *8*, 10729/1–10.

Introduction

Heck, Negishi, and Suzuki were awarded the Nobel prize in chemistry in 2010 "for palladium-catalyzed cross-couplings in organic synthesis".[1] Cross-coupling reactions represent one of the most efficient methods for carbon-carbon bond formation and are indispensable for chemists.[2] Transition metals, mainly based on palladium complexes, are generally employed for cross-coupling chemistry due to their efficiency and broad substrate scope. The first, and generally rate-determining, step in the catalytic cycle of a cross-coupling reaction is the activation of a bond (Scheme 1) via an oxidation addition to the transition-metal complex (Scheme 2).



Scheme 1. Oxidative addition and reductive elimination.



Scheme 2. General mechanism for cross-coupling reactions.

In this exercise, you will study the bond activation via oxidative addition of a palladium catalyst in $H_3C–X + PdL_n$ model systems (X = H, CH_3, Cl; L_n = no ligand, $(PH_3)_2$, $PH_2CH_2PH_2$) using relativistic density functional theory at ZORA-BLYP/TZ2P. The two goals of this project are to screen to oxidation addition of 1) $H_3C–X + PdL_n$ model systems (X = H, CH_3, Cl; L_n = no ligand)

and then 2) $H_3C–X$ + PdL_n model systems (X = Cl; L_n = no ligand, $(PH_3)_2$, $PH_2CH_2PH_2$). The first goal of the project assesses the activation of various bonds by a bare palladium atom, while the second assesses the effect of bite angle on the activation of a C–Cl bond. The analyses will be carried out within the framework of Kohn-Sham molecular orbital (KS-MO) theory, in combination with a quantitative energy decomposition analysis (EDA) analysis. The primary objectives of this exercise are to obtain a quantitative understanding of the reactivity trends and also to uncover the physical factors controlling the bond activation process.

Step 1.1. Optimize stationary points (reactants, reactant complex, product) and compute ΔE_{rxn}

First, optimize the structures of the stationary points (reactants, reactant complex, and product) on the potential energy surface at ZORA-BLYP/TZ2P to their energy minima. A frequency calculation will confirm the nature of the stationary points, as energy minima have zero imaginary frequencies. The reaction energy (ΔE_{rxn}) is computed by the difference in energy between the product and the separated reactants. Which $H_3C–X$ bond (X = H, C, Cl) activation is most favorable from a thermodynamic perspective? What effect do the ligands (L_n = no ligand, $(PH_3)_2$, $PH_2CH_2PH_2$) play on the thermodynamics?

Technical note
An example input files for a geometry is provided in the appendix.
Instructions:
i) Launch ADFinput.
ii) Draw the molecule/import coordinates from literature. Go to Detail → Run Script to copy the coordinates and paste them in the "Geometry optimization" input file.
iii) Run the geometry optimization together with a frequency calculation.
iv) Open the generated .t21 file using ADFspectra to see if the optimized structures are actual energy minima. All peaks of the IR spectrum should point in the same direction.

Step 1.2. Optimize stationary points (transition states) and compute $\Delta E^{‡}$

Then, optimize the transition state structure on the potential energy surface at ZORA-BLYP/TZ2P to an energy maximum (first-order saddle point). Again, a frequency calculation can confirm the nature of the stationary points, and a transition states will have a single imaginary frequency. **Tip:** Visualize this imaginary frequency and ensure that the corresponding molecular motion corresponds to the oxidative addition process! The activation barrier ($\Delta E^{‡}$) is computed by the difference in energy between the transition state and the separated reactants. **Note:** A linear transit (LT) calculation can be useful for obtaining an approximate transition state geometry. LT calculations scan the potential energy surface given a relevant constraint (such as a bond distance or bond angle). A LT can be run from a product towards the reactants or from a reactant complex to the product (select which ever approach is most suitable for your reaction). Which $H_3C–X$ bond (X = H, C, Cl) is easiest to activate from a kinetic

perspective? What effect do the ligands (L_n = no ligand, $(PH_3)_2$, $PH_2CH_2PH_2$) play on the kinetics? Is it kinetically advantageous use a bidentate ligand (L_n = $PH_2CH_2PH_2$)?

Technical note

Example input files for a transition state optimization and linear transit are provided in the appendix.

Instructions:

i) Launch ADFinput.

ii) Import the coordinates of the product(complex).

iii) Locate the bonds that change during the course of the reaction. For example, the dissociation of a C–X bond by oxidative addition.

iv) Set up geometry constraints by changing the following line to the LT input file:

```
CONSTRAINTS
   DIST X Y start=A end=B
END
```

X and Y are the atom numbers of the atoms involved in the bond that change during the reaction. A and B are the initial and final X–Y bond distances, i.e., the distance in the respective reactant(complex) and product(complex).

v) Run the linear transit in order to simulate the reaction pathway within the chosen constraints.

vi) Open the resulting .t21 file using ADFmovie to locate the approximate TS. Go to Graph → Energy to display the simulated PES. Go to view → Converged geometries only in order to only display the converged geometries. The highest point of the energy graph is the geometry that closely resembles your transition state. Save this geometry by clicking on this point of the energy graph, followed by file → save geometry. This will generate a text file including the coordinates.

vii) Copy the coordinates of step vi to the TSRC input file and specify a reaction coordinate along which the TS will be searched for:

```
TSRC
   DIST X Y [fac]
END
```

Here, X and Y are the atom numbers of the atoms involved in the bond that change during the reaction, which, most often, is the same bond as specified in step iv. Followed by a factor [fac], which can be either 1.0 or –1.0, defining an in- or decrease of the X–Y bond distance, respectively.

viii) Run the TSRC in order to find the transition state together with the corresponding hessian.

ix) Open the generated .t21 file using ADFspectra to check if you found an actual TS. There should be one peak with an imaginary frequency, i.e., one peak point downwards. Click on this peak in order to see the corresponding normal mode, which should be mode of the reaction.

Step 2. Perform intrinsic reaction coordinate (IRC) calculations

Next, perform intrinsic reaction coordinate (IRC) calculations to obtain the potential energy surface that connects the transition state to both the reactants and product. The molecular motion along the IRC surface will correspond to the vibration of the imaginary frequency in the transition state structure. **Note:** These IRC calculations use a transition state you found in step 1.2 as an input.

Technical note

An example input file for an intrinsic reaction coordinate (IRC) calculation is provided in the appendix.
Instructions:
i) Import the coordinates of the transition state into the IRC input file.
ii) By specifying backward or forward in the geometry block you can run the IRC calculations parallel to the adjacent local minima, meaning that the pathway from the TS to the reactant(complex) and to the product(complex) are calculated separately.

```
Geometry
   IRC [Backward/Forward] POINTS=A STEP=B
End
```

Additionally, you should note the number of IRC points A computed for the run, as well as, the step length B when proceeding from one IRC point to another. Specify 30-50 points and a step size of (0.8).
iii) In order to restart from the hessian calculated during the TSRC calculations, locate the .t21 file of the TSRC calculation by directing to the respective .t21 using the restart key.

```
Restart[pathway]/TSRC.t21
```

iv) Run the IRC calculation to obtain the PES.
v) Check the generated .out file to see if the IRC calculation has reached the local minimum. The complete PES is calculated when the .out file ends with the statement "finishing IRC path Back/Forward". If this statement is not present in the .out file you should continue to perform IRC calculations restarting from the .t21 file of the previous IRC calculation until this statement is present.

Step 3.1. Perform an Activation Strain Analysis (ASA)

Next, perform an activation strain analysis[3] (ASA) on each point along the IRC using the PyFrag 2019 program. This quantitative analysis will reveal the physical factors at play which govern the molecular reactivity and will allow us to understand why certain reactions proceed faster than others. This analysis involves decomposing the potential energy surface $\Delta E(\zeta)$ along the reaction coordinate ζ into the strain $\Delta E_{strain}(\zeta)$ associated with deforming the reactants from their equilibrium geometry and the interaction $\Delta E_{int}(\zeta)$ between the deformed reactants (Figure 1).

$$\Delta E(\zeta) = \Delta E_{strain}(\zeta) + \Delta E_{int}(\zeta) \quad (1)$$

The $\Delta E_{strain}(\zeta)$ is determined by the rigidity of the reactants and by the extent to which they must distort in order to achieve the transition state geometry. The $\Delta E_{int}(\zeta)$ is usually stabilizing and is related to the electronic structure of the reactants and how they are mutually oriented over the course of the reaction.

In the activation strain and energy decomposition plots, you should project the IRC onto the C–X bond stretch (actual length minus the equilibrium bond length) that is being activated during the reaction. This resulting reaction coordinate ζ undergoes a well-defined change in the course of the reaction from the reactant complex to the transition state and products.

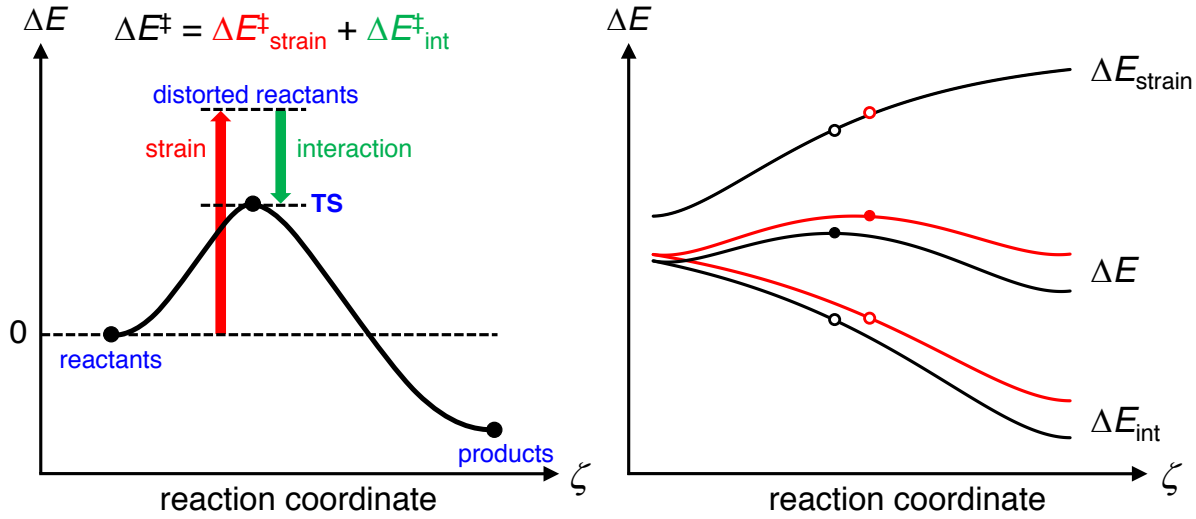


Figure 1. Activation strain analysis a) at the transition state and b) along a reaction coordinate.

Make two activation strain diagrams (ASD) corresponding to the oxidation addition of 1) H_3C–X + PdL_n model systems (X = H, CH_3, Cl; L_n = no ligand) and then 2) H_3C–X + PdL_n model systems (X = Cl; L_n = no ligand, $(PH_3)_2$, $PH_2CH_2PH_2$). Analyze both ASDs and determine whether the strain (ΔE_{strain}) or interaction energy (ΔE_{int}) term(s) governs the trends in barrier height (ΔE). If the ΔE_{strain} determines the trend in ΔE, then decompose the ΔE_{strain} into the $\Delta E_{strain(substrate)}$ and $\Delta E_{strain(cat)}$. This decomposition will reveal the origin for the trend in ΔE_{strain}, which you should then rationalize using your chemical intuition. On the other hand, if the ΔE_{int} determines the trend in ΔE, then proceed to step 3.2. in order to decompose the energy term into its components.

Step 3.2. Perform an Energy Decomposition Analysis (EDA)

Perform an energy decomposition analysis (EDA) on each point along the IRC using the PyFrag 2019 program. This data should already be printed in the text file generated by PyFrag 2019 after completion of step 3.1.

Energy Decomposition Analysis

The interaction $\Delta E_{int}(\zeta)$ between the deformed reactants can be decomposed into three physically meaningful terms, in the conceptual framework provided by the Kohn–Sham molecular orbital (KS-MO) model.[4]

$$\Delta E_{int}(\zeta) = \Delta V_{elstat}(\zeta) + \Delta E_{Pauli}(\zeta) + \Delta E_{oi}(\zeta) \quad (2)$$

The $\Delta V_{elstat}(\zeta)$ term corresponds to the classical electrostatic interaction between unperturbed charge distributions $\rho_A(r) + \rho_B(r)$ of the deformed fragments A and B and is usually attractive. The Pauli repulsion $\Delta E_{Pauli}(\zeta)$ comprises the destabilizing interactions between occupied orbitals

and is responsible for any steric repulsion. The orbital interaction ΔE_{oi} accounts for charge transfer (interaction between occupied orbitals on one fragment with unoccupied orbitals of the other fragment, including HOMO–LUMO interactions) and polarization (empty–occupied orbitals mixing on one fragment due to the presence of another fragment).

Make two Energy Decomposition Analysis diagrams corresponding to the oxidation addition of 1) $H_3C–X + PdL_n$ model systems (X = H, CH_3, Cl; L_n = no ligand) and then 2) $H_3C–X + PdL_n$ model systems (X = Cl; L_n = no ligand, $(PH_3)_2$, $PH_2CH_2PH_2$). Analyze both figures and determine whether the electrostatics (ΔV_{elstat}), Pauli repulsion (ΔE_{Pauli}), or orbital interaction (ΔE_{OI}) term(s) governs the trends in interaction energy (ΔE_{int}).

Technical note
The PyFrag 2019 program can be downloaded from:
https://pyfragdocument.readthedocs.io/en/latest/install.html
Additional details can be found at: https://pyfragdocument.readthedocs.io/en/latest/pyfragparameter.html
An example can be found at: https://pyfragdocument.readthedocs.io/en/latest/standalone.html

Instructions.
i) Install PyFrag 2019 by following the link above and provided documentation.
ii) Make a directory containing the PyFrag 2019 input file and the .t21 file of the backward or forward IRC calculation.
iii) Open the PyFrag 2019 input file and allocate, in the PyFrag block, the .t21 file of the IRC calculation using the following key.

```
irct21 [pathway]/IRC.t21
```

iv) Specify the two interacting fragments, for example, the catalyst and the substrate:

```
fragment [#atomnrs_fragment1]
fragment [#atomnrs_fragment2]
```

Here, you supply for each fragment a list of the numbers for the atoms as they appear in the IRC file.
v) In order to print the strain energy, you should specify the equilibrium energies of your fragment, which was calculated in Step 1.1.

```
strain [equil_energy_fragment1]
strain [equil_energy_fragment2]
```

The equilibrium energy will simply be subtracted from the energy of the fragment in question. PyFrag 2019 will print the individual strain values for each fragment, together with, the total strain energy.
vi) To plot the activation strain analysis and energy decomposition analysis data, we need to have a reaction coordinate. A common reaction coordinates is the dissociating C–X bond by a oxidative addition reaction.

```
bondlength X Y [bond_diff]
```

Here, X and Y are the atom numbers of the atoms involved in the bond that change during the reaction, which, most often are the same atoms as specified in step 1.2. Followed by the initial bond length [bond_diff] between atom X and Y. By defining the [bond_diff] PyFrag 2019 subtracts this value from the actual bond length.

vii) Run the PyFrag 2019 input file to obtain the activation strain analysis and energy decomposition analysis data, which will be printed in the resulting .txt file.

Step 4. Analyzing the Energy Decomposition Analysis Terms

Once you determine the operative Energy Decomposition Analysis term that governs the trends in interaction energy, you should dig deeper into it to establish a physical mechanism to explain the reactivity trends of your model oxidative addition reactions.

If ΔV_{elstat} determine the trend in ΔE_{int}, perform a charge analysis by inspecting the computed Voronoi Deformation Density (VDD) charges.

If ΔE_{oi} determine the trend in ΔE_{int}, perform a Kohn-Sham Molecular Orbital (KS-MO) analysis. First, visualize the orbitals of the separated monomers with ADFview and consider which donor-acceptor interactions might be possible. Next, open the MO diagram of the complex with ADFlevels, and analyze which fragment orbitals participate in HOMO-LUMO interactions. Analyze their mutual overlap and gross populations (you can print these using PyFrag 2019), and write down their energy difference (HOMO-LUMO gap). Rationalize the differences in orbital interaction strength?

If ΔE_{Pauli} determine the trend in ΔE_{int}, again, perform a Kohn-Sham Molecular Orbital (KS-MO) analysis. First, visualize the orbitals of the separated monomers with ADFview and consider which four electron-two orbital interactions might be possible. Next, open the MO diagram of the complex with ADFlevels, and analyze which fragment orbitals participate in HOMO-HOMO interactions. Analyze their mutual overlap (you can print these using PyFrag 2019), and rationalize the differences in Pauli repulsion.

Appendix

Queues on Bazis cluster
Normal queue:
#SBATCH -p defq

Special queue for the course:
#SBATCH -p studentq

Input file: Geometry optimization

```
#!/bin/bash
#SBATCH -p defq
export SCM_TMPDIR=/local/datastore0/$USER/$SLURM_JOBID
srun mkdir -p $SCM_TMPDIR
chmod 700 $SCM_TMPDIR
cd $SCM_TMPDIR
export TC_SUBMISSION_DIR=$SLURM_SUBMIT_DIR

$ADFBIN/adf <<eor>$SLURM_SUBMIT_DIR/$SLURM_JOB_NAME.out

RELATIVISTIC SCALAR ZORA

XC
  GGA blyp
END

BASIS
  TYPE TZ2P
  CORE large
END

ANALYTICALFREQ
END
ScanFreq -9999 0 Num=6 Disrad=0.0035

SCF
  iterations 250
END

Geometry
  Iterations 300
  Optim Delocal
  CONVERGE 0.001
End

SYMMETRY nosym
CHARGE 0 0

ZLMFIT
  Quality normal
END

BECKEGRID
  Quality good
End

ATOMS
END

ENDINPUT
eor

cp TAPE21 $SLURM_SUBMIT_DIR/$SLURM_JOB_NAME.t21
```

Input file: Transition state (TS) optimization

```
#!/bin/bash
#SBATCH -p defq
export SCM_TMPDIR=/local/datastore0/$USER/$SLURM_JOBID
srun mkdir -p $SCM_TMPDIR
chmod 700 $SCM_TMPDIR
cd $SCM_TMPDIR
export TC_SUBMISSION_DIR=$SLURM_SUBMIT_DIR

$ADFBIN/adf <<eor>$SLURM_SUBMIT_DIR/$SLURM_JOB_NAME.out

RELATIVISTIC SCALAR ZORA

XC
  GGA blyp
END

BASIS
  TYPE TZ2P
  CORE large
END

ANALYTICALFREQ
END

SCF
  iterations 250
END

Geometry
  transitionstate mode=1
  Iterations 300
  Optim Delocal
  CONVERGE 0.001
End

TSRC
   DIST X Y [fac]
END

SYMMETRY nosym
CHARGE 0 0

ZLMFIT
  Quality normal
END

BECKEGRID
  Quality good
End

ATOMS
END

ENDINPUT
eor

cp TAPE21 $SLURM_SUBMIT_DIR/$SLURM_JOB_NAME.t21
```

Input file: Linear Transit (LT)

```
#!/bin/bash
#SBATCH -p defq
export SCM_TMPDIR=/local/datastore0/$USER/$SLURM_JOBID
srun mkdir -p $SCM_TMPDIR
chmod 700 $SCM_TMPDIR
cd $SCM_TMPDIR
export TC_SUBMISSION_DIR=$SLURM_SUBMIT_DIR

$ADFBIN/adf <<eor>$SLURM_SUBMIT_DIR/$SLURM_JOB_NAME.out
```

```
RELATIVISTIC SCALAR ZORA

XC
  GGA blyp
END

BASIS
  TYPE TZ2P
  CORE large
END

SCF
  iterations 250
END

Geometry
  LinearTransit 8
  Constraints PartialConverge
  Iterations 999
  Optim Cartesian
  CONVERGE 0.001
End

CONSTRAINTS
   DIST X Y start=A end=B
END

SYMMETRY nosym
CHARGE 0 0

ZLMFIT
  Quality normal
END

BECKEGRID
  Quality normal
End

ATOMS
END

ENDINPUT
eor

cp TAPE21 $SLURM_SUBMIT_DIR/$SLURM_JOB_NAME.t21
```

Input file: Intrinsic reaction coordinate (IRC)

```
#!/bin/bash
#SBATCH -p defq
export SCM_TMPDIR=/local/datastore0/$USER/$SLURM_JOBID
srun mkdir -p $SCM_TMPDIR
chmod 700 $SCM_TMPDIR
cd $SCM_TMPDIR
export TC_SUBMISSION_DIR=$SLURM_SUBMIT_DIR

$ADFBIN/adf <<eor>$SLURM_SUBMIT_DIR/$SLURM_JOB_NAME.out

RELATIVISTIC SCALAR ZORA

XC
  GGA blyp
END

BASIS
  TYPE TZ2P
  CORE large
END
```

```
SCF
  iterations 250
END

Geometry
   Irc Forward Points=50 Step=0.8
   Optim Cartesian
   Iterations 200
   Converge Grad=0.001
End

SYMMETRY nosym
CHARGE 0 0

ZLMFIT
  Quality normal
END

BECKEGRID
  Quality normal
End

ATOMS
END

ENDINPUT
eor

cp TAPE21 $SLURM_SUBMIT_DIR/$SLURM_JOB_NAME.t21
```

Input file: PyFrag 2019

```
JOBSUB

#!/bin/bash
#SBATCH -p defq
#SBATCH -J NNC
#SBATCH -N 1
#SBATCH -t 24:00:00
#SBATCH --ntasks-per-node=24
#SBATCH --output=%job.stdout
#SBATCH --error=%job.stdout
export NSCM=24

JOBSUB END

PyFrag

irct21 /home/FILL IN PATH/irc.t21
fragment  ATOM# ATOM# ATOM#
fragment  ATOM# ATOM# ATOM#
strain    -ENERGY
strain    -ENERGY
bondlength ATOM# ATOM#  [equilibrium bond length]

PyFrag END

ADF

BASIS
  TYPE TZ2P
  CORE large
END

XC
  GGA blyp
END

relativistic SCALAR ZORA

SCF
  iterations 250
END
```

```
ZLMFIT
  Quality normal
END

BECKEGRID
  Quality good
End

SYMMETRY nosym
CHARGE 0 0

ADF END
```

Additional References

[1] a) "The Nobel Prize in Chemistry 2010—Press Release". http://nobelprize.org/nobel_prizes/chemistry/laureates/ 2010/press.html ; b) A. Suzuki, *Angew. Chem. Int. Ed.* 2011, *50*, 6722; c) E.-I. Negishi, *Angew. Chem. Int. Ed.* 2011, *50*, 6738.

[2] J. F. Hartwig, Organotransition Metal Chemistry: From Bonding to Catalysis, 1st Ed. University Science Books, Sausalito, 2010.

[3] a) F. M. Bickelhaupt, K. N. Houk, *Angew. Chem. Int. Ed.* 2017, *56*, 10070; *Angew. Chem.* 2017, *129*, 10204; b) L. P. Wolters, F. M. Bickelhaupt, *WIRES Comput. Mol. Sci.* 2015, *5*, 324; c) I. Fernández, F. M. Bickelhaupt, *Chem. Soc. Rev.* 2014, *43*, 4953; d) W.-J. van Zeist, F. M. Bickelhaupt, *Org. Biomol. Chem.* 2010, *8*, 3118; e) F. M. Bickelhaupt, *J. Comput. Chem.* 1999, *20*, 114.

[4] a) T. Ziegler, A. Rauk, *Inorg. Chem.* 1979, *18*, 1755–1759; b) F. M. Bickelhaupt, N. M. M. Nibbering, E. M. van Wezenbeek, E. J. Baerends, *J. Phys. Chem.* 1992, *96*, 4864–4873; c) F. M. Bickelhaupt, A. Diefenbach, S. P. de Visser, L. J. de Koning, N. M. M. Nibbering, *J. Phys. Chem. A* 1998, *102*, 9549–9553; d) E. J. Baerends, O. V. Gritsenko, *J. Phys. Chem. A* 1997, *101*, 5383–5403.