

Supporting Information:

How Hydrogen Bonding Amplifies Isomeric Differences in Pyridones Towards Strong Changes in Acidity and Tautomerism

Robby Büchner,^{*,†} Mattis Fondell,[‡] Eric J. Mascarenhas,^{‡,†} Annette Pietzsch,[‡]

Vinícius Vaz da Cruz,^{*,‡} and Alexander Föhlisch^{‡,†}

[†]*Institute of Physics and Astronomy, University of Potsdam, Karl-Liebknecht-Str. 24-25,
14476 Potsdam, Germany*

[‡]*Institute for Methods and Instrumentation for Synchrotron Radiation Research,
Helmholtz-Zentrum Berlin für Materialien und Energie, Albert-Einstein-Str. 15, 12489
Berlin, Germany*

E-mail: robby.buechner@helmholtz-berlin.de; vinicius.vaz_da_cruz@helmholtz-berlin.de

Resonance structures of the Pyridone isomers

The resonance structures of the *ortho*, *meta*, and *para* Pyridone isomers are shown in Fig. S1.

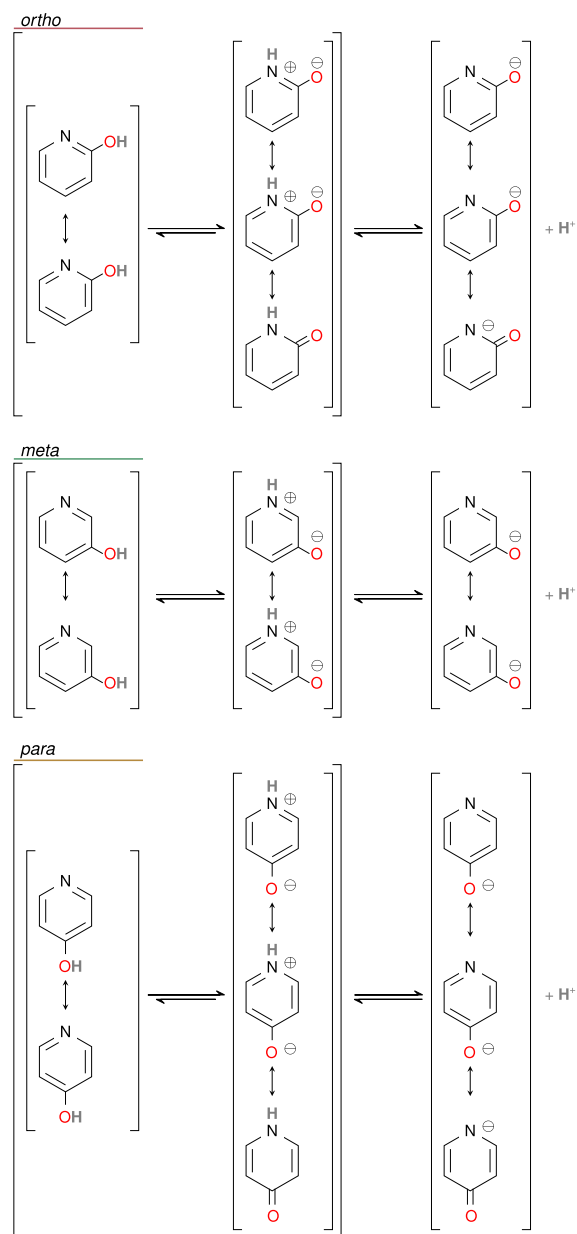


Figure S1: Resonance structures of the Hydroxypyridine (left) and Pyridone (middle) tautomers along with the fully deprotonated species (right).

Details of the Molecular Dynamics Simulations

The following procedure was carried out for all nine chemical species under study: Initially, a cubic box of 3.4 nm length comprising the chemical species of interest has been generated, then one Cl^- and K^+ counterion was added to the box for positively charged (PyH^+) and negatively charged molecules (2PO^- , 3PO^- , 4PO^-), respectively. The remaining space was filled with solvent molecules by using the *gmx_solvate* tool from the Gromacs package.^{S1} All calculations used periodic boundary conditions. The temperature was controlled by a modified Berendsen thermostat (0.1 ps time constant) and in NPT runs the Parrinello-Rahman pressure-coupling (2 ps time constant) was used. For the calculation of the Coulomb and van der Waals term a cut-off of 1.4 nm was employed, while long-range electrostatics were treated via the particle mesh Ewald (PME) procedure. The energy of the initially generated system was minimized and subsequently the box was equilibrated in two steps: Firstly, an NVT equilibration at $T = 298$ K was run for 500 ps ($\Delta t = 0.5$ fs), followed by an NPT equilibration at $T = 298$ K and $P = 1$ bar, which was also run for 500 ps ($\Delta t = 0.5$ fs). The coordinates of the complex were constrained to the center of the box throughout the equilibration. Finally, a production NPT run of 10 ns ($\Delta t = 0.5$ fs, $T = 298$ K and $P = 1$ bar) was performed from which snapshots were collected every 1 ps. The final run was used for analysis of the radial distribution functions (see Fig. S2), hydrogen bonding properties (see below) and solvent mass-density plots (in the main article).

Force field and chelpg charges

The parameters for the intramolecular degrees of freedom as well as the Lennard-Jones non-bonded interactions were taken from the OPLS-aa^{S2} force field by choosing the closest match to the molecules at hand. Since the charges used for the Coulomb interactions are not transferable as the other parameters, we chose to derive them for each molecule using the chelpg^{S3} procedure, as implemented in the *orca_chelpg* utility program. The charges were

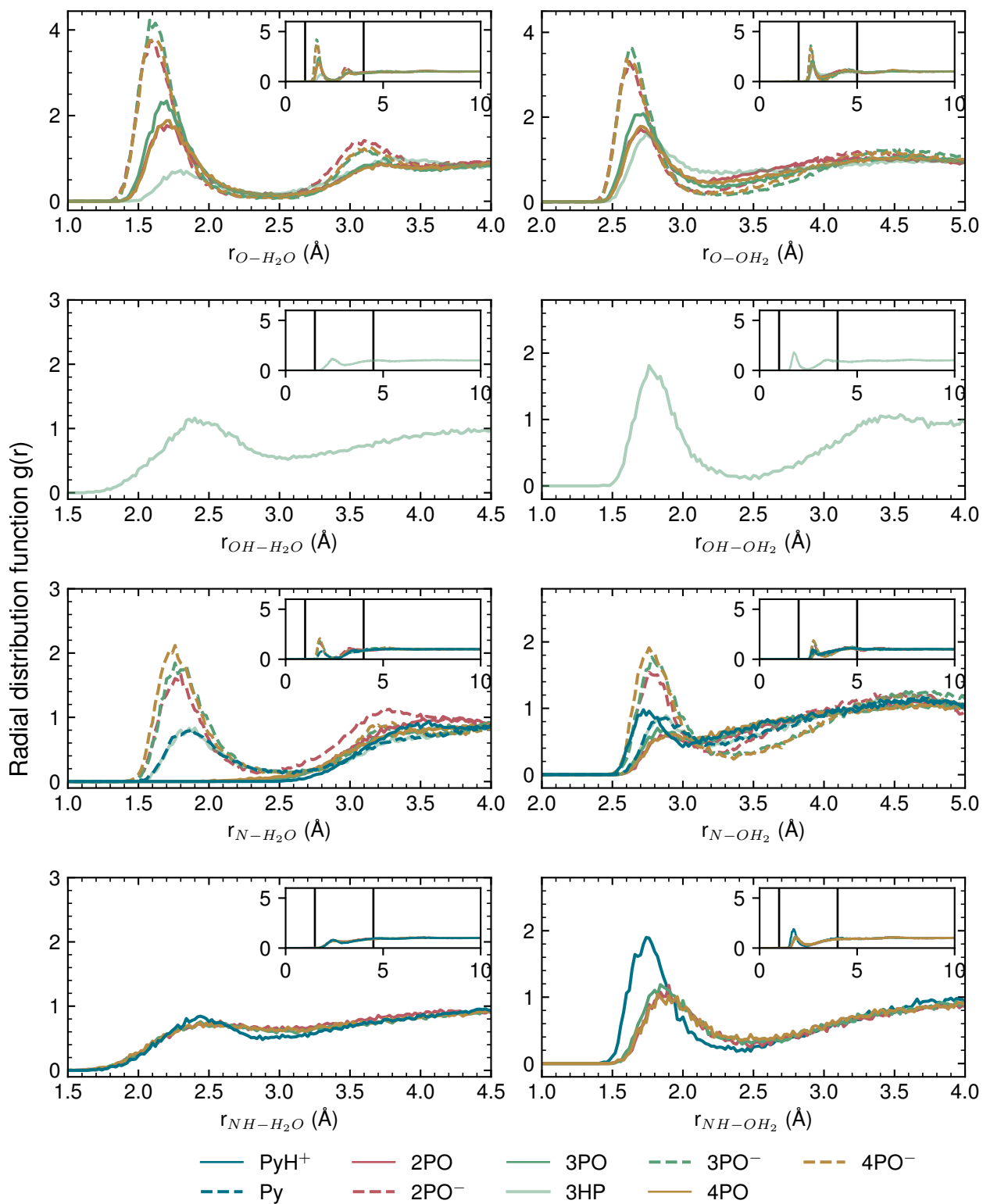


Figure S2: Radial distribution functions between oxygen (1st row), hydrogen (2nd, 4th row), or nitrogen (3rd row) of the sample and hydrogen (left) or oxygen (right) of water.

derived based on structures optimized at the RI-MP2 level of theory with the aug-cc-pVTZ basis set and the aug-cc-pVTZ/C auxiliary basis set. The calculations used CPCM.^{S4} The full set of charges obtained is shown in Tab. S1.

Table S1: Chelpg charges used for the description of the electrostatic interactions in the MD simulations. For all molecules the nitrogen atom is labeled N1, then all carbon atoms are numbered clockwise. The numbering of the oxygen and hydrogen atoms is taken as the same number of the respective atom to which they are bonded.

PyH ⁺		Py		2PO		2PO ⁻			
label	q (e)	label	q (e)	label	q (e)	label	q (e)		
N1	-0.089	N1	-0.665	N1	-0.310	N1	-0.891		
H1	0.341	C2	0.482	H1	0.303	C2	1.173		
C2	-0.008	C3	-0.530	C2	0.646	C3	-0.750		
C3	-0.058	C4	0.272	C3	-0.333	C4	0.265		
C4	-0.016	C5	-0.530	C4	0.009	C5	-0.744		
C5	-0.059	C6	0.482	C5	-0.276	C6	0.466		
C6	-0.008	H2	0.020	C6	-0.046	H3	0.168		
H2	0.184	H3	0.191	H3	0.171	H4	0.029		
H3	0.179	H4	0.067	H4	0.123	H5	0.171		
H4	0.170	H5	0.191	H5	0.164	H6	-0.016		
H5	0.180	H6	0.020	H6	0.155	O2	-0.871		
H6	0.184			O2	-0.606				
3PO		3PO ⁻		3HP		4PO		4PO ⁻	
label	q (e)	label	q (e)	label	q (e)	label	q (e)	label	q (e)
N1	-0.059	N1	-0.729	N1	-0.636	N1	-0.257	N1	-0.847
H1	0.304	C2	0.283	C2	0.343	H1	0.311	C2	0.494
C2	-0.259	C3	0.252	C3	0.071	C2	-0.019	C3	-0.837
C3	0.606	C4	0.009	C4	-0.005	C3	-0.378	C4	1.050
C4	-0.292	C5	-0.573	C5	-0.441	C4	0.701	C5	-0.837
C5	-0.063	C6	0.312	C6	0.377	C5	-0.367	C6	0.492
C6	-0.229	H2	-0.005	H2	0.077	C6	-0.027	H2	-0.020
H2	0.163	H4	0.060	H4	0.115	H2	0.145	H3	0.187
H4	0.160	H5	0.158	H5	0.189	H3	0.177	H5	0.187
H5	0.142	H6	-0.007	H6	0.044	H5	0.173	H6	-0.019
H6	0.165	O3	-0.760	O3	-0.548	H6	0.148	O4	-0.850
O3	-0.638			H3	0.414	O4	-0.607		

Hydrogen bonding properties

The analysis of the hydrogen bonding properties was carried out by examining the radial distribution functions, obtained with the *gmx_rdf* tool, as well as analysing hydrogen bond (HB) statistics with the *gmx_hbond* tool included in the Gromacs package. The full set of HB parameters is shown in Tab. S2

Table S2: Hydrogen bonding parameters extracted from the MD simulations in aqueous solution. The r_{NH} distance is obtained from the maximum of the $g_{XH}(r)$ and $g_{HO}(r)$ pair-correlation functions. The number of HBs (n_{HB}) is defined via the X=N,O and the water OH bond for $\angle XHO < 20^\circ$ and $r_{X-O} < 3.5 \text{ \AA}$.

Molecule	r_{N-H}	$r_{N-O} \text{ (\AA)}$	$\angle NOH \text{ (}^\circ\text{)}$	n_{HB}
Py	1.87	2.92 ± 0.18	11.16 ± 4.91	0.90 ± 0.60
2PO ⁻	1.79	2.86 ± 0.17	10.01 ± 4.78	1.58 ± 0.58
3PO ⁻	1.80	2.88 ± 0.18	10.16 ± 4.83	1.92 ± 0.63
4PO ⁻	1.77	2.86 ± 0.18	9.71 ± 4.74	2.09 ± 0.61
3HP	1.88	2.93 ± 0.18	11.22 ± 4.88	0.87 ± 0.61
Molecule	r_{NH-O}	$r_{N-O} \text{ (\AA)}$	$\angle NHO \text{ (}^\circ\text{)}$	n_{HB}
PyH ⁺	1.76	2.78 ± 0.13	10.86 ± 4.89	0.72 ± 0.45
2PO	1.90	2.95 ± 0.19	11.48 ± 4.91	0.60 ± 0.50
3PO	1.88	2.91 ± 0.19	11.61 ± 4.87	0.60 ± 0.51
4PO	1.90	2.95 ± 0.20	11.69 ± 4.88	0.58 ± 0.53
Molecule	r_{CO-H}	$r_{CO-O} \text{ (\AA)}$	$\angle OOH \text{ (}^\circ\text{)}$	n_{HB}
2PO	1.72	2.78 ± 0.17	10.50 ± 4.84	1.59 ± 0.66
3PO	1.71	2.77 ± 0.17	10.24 ± 4.82	1.96 ± 0.68
4PO	1.72	2.79 ± 0.17	10.57 ± 4.91	1.66 ± 0.69
2PO ⁻	1.58	2.70 ± 0.16	9.00 ± 4.59	2.76 ± 0.54
3PO ⁻	1.58	2.71 ± 0.16	8.92 ± 4.55	3.11 ± 0.56
4PO ⁻	1.62	2.70 ± 0.16	9.00 ± 4.60	2.87 ± 0.55
3HP	1.80	2.88 ± 0.19	11.35 ± 4.89	0.72 ± 0.58
Molecule	r_{OH-O}	$r_{CO-O} \text{ (\AA)}$	$\angle OHO \text{ (}^\circ\text{)}$	n_{HB}
3HP	1.80	2.83 ± 0.18	10.88 ± 4.87	1.52 ± 0.71

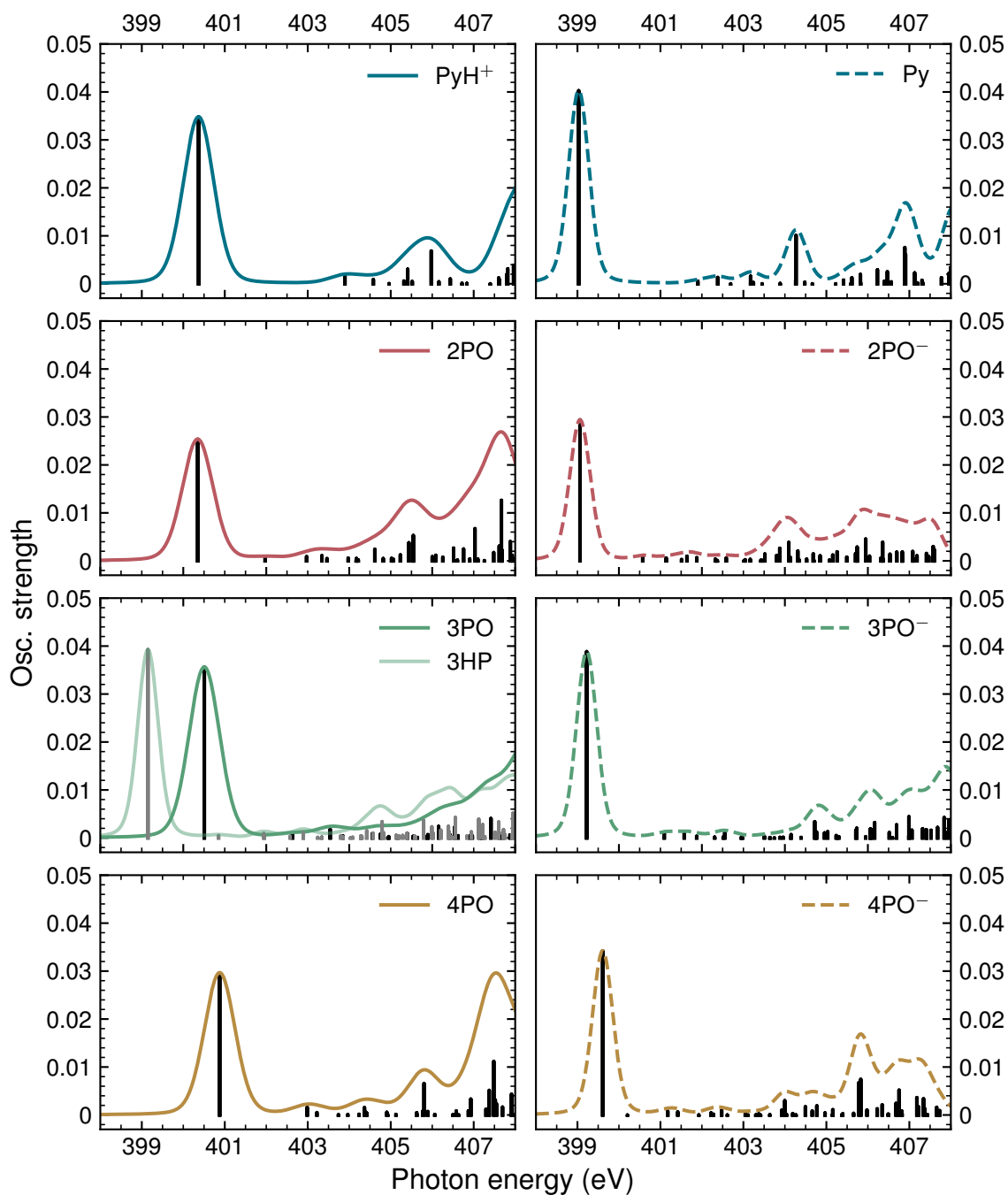


Figure S3: X-ray absorption at the N K -edge as calculated by the TD-DFT method. The energy axis is shifted by 11.135 eV to ease the comparison with the experimental spectra in the main article. Transition moments are shown as black bars. For the plotted spectra a lifetime broadening of 0.13 eV^{S5} and an experimental broadening of 0.51 eV (deprotonated nitrogen) or 0.80 eV (protonated nitrogen) have been used.

TD-DFT

As described in the computational details section of the main article, TD-DFT calculations were performed on the optimized geometries with the minimally-solvated models resulting from the MD simulation. The TD-DFT calculations were carried out with PBE0 hybrid functionals^{S6} utilizing the def2-QZVPPD^{S7,S8} basis and def2/J^{S9} auxiliary basis set with the RIJCOSX^{S10} approximation. CPCM^{S4} was used to account for bulk-liquid effects. For numerical integration the ORCA^{S11} Grid7 (and GridX9 as COSX grid) were used.

N *K*-edge absorption spectra (see Fig. S3) were obtained by applying a Voigt function to every transition moment. The Gaussian broadening results from a global fit of the experimental π^* resonance of all molecules with the same nitrogen protonation state and a fixed Lorentzian FWHM of 0.13 eV.^{S5} Additionally the spectra were shifted according to the difference of the TD-DFT and experimental π^* resonance of Py.

References

- (S1) Lindahl,; Abraham,; Hess,; van der Spoel, GROMACS 2019 source code. <https://doi.org/10.5281/zenodo.2424363>.
- (S2) Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J. Development and testing of the OPLS all-atom force field on conformational energetics and properties of organic liquids. *J. Am. Chem. Soc.* **1996**, *118*, 11225–11236.
- (S3) Breneman, C. M.; Wiberg, K. B. Determining atom-centered monopoles from molecular electrostatic potentials. The need for high sampling density in formamide conformational analysis. *J. Comput. Chem.* **1990**, *11*, 361–373.
- (S4) Barone, V.; Cossi, M. Quantum calculation of molecular energies and energy gradients in solution by a conductor solvent model. *J. Phys. Chem. A* **1998**, *102*, 1995–2001.

- (S5) Nicolas, C.; Miron, C. Lifetime broadening of core-excited and -ionized states. *J. Electron Spectrosc. Relat. Phenom.* **2012**, *185*, 267 – 272.
- (S6) Adamo, C.; Barone, V. Toward reliable density functional methods without adjustable parameters: The PBE0 model. *J. Chem. Phys.* **1999**, *110*, 6158–6170.
- (S7) Weigend, F.; Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305.
- (S8) Rappoport, D.; Furche, F. Property-optimized Gaussian basis sets for molecular response calculations. *J. Chem. Phys.* **2010**, *133*, 134105.
- (S9) Weigend, F. Accurate Coulomb-fitting basis sets for H to Rn. *Phys. Chem. Chem. Phys.* **2006**, *8*, 1057–1065.
- (S10) Neese, F.; Wennmohs, F.; Hansen, A.; Becker, U. Efficient, approximate and parallel Hartree-Fock and hybrid DFT calculations. A chain-of-spheres-algorithm for the Hartree-Fock exchange. *Chem. Phys.* **2009**, *356*, 98 – 109.
- (S11) Neese, F. The ORCA program system. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2012**, *2*, 73–78.