Electronic structure of sulfur-nitrogen containing compounds: correlations with theory and chemical reactivity

by

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Abstract

Molecules containing sulfur-nitrogen bonds, such as sulfonamides, have long been of interest due to their many uses and chemical properties, including the potential release of nitric oxide and nitroxy1. Understanding the factors that cause sulfonamide reactivity is crucial, yet their inherent electronic complexity have made them difficult to examine. In this thesis, sulfur K-edge x-ray absorption spectroscopy (XAS) is used in conjunction with density functional theory (DFT) to determine the role of electronic transmission effects through the sulfur-nitrogen bond. A systematic deconstruction of the elements within the sulfonamide moiety is used as an approach to understand critical factors that dictate electronic structure.

First, the effect of oxidation state changes and variations in R-group in sulfoxamides, sulfonamides and sulfonamides on intramolecular bonding are explored. Next, N-hydroxylation of the sulfonamide amide, in both alkyl sulfonamides and a series of para-substituted aryl sulfonamides with varying Hammett para-sigma constants are studied using structure-function relationships, in conjunction with DFT, to understand the role of electron donation and withdrawal to the sulfonamide moiety. The outcome of these modifications on the sulfonamide framework lead to better insight towards directed drug design and its influence on nitroxy1 and nitric oxide release.
Preface

All of the DFT calculations in chapters three and five were performed by me using ORCA quantum chemistry program developed by Frank Neese at the University of Bonn. Two compounds in chapter three were synthesized in the laboratory of Scott Bohle at McGill University: tert-butane sulfinamide and potassium dinitrososulfite. The sulfonamides used in chapters three and four were purchased from Sigma-Aldrich. I synthesized all of the N-hydroxy sulfonamide compounds used in chapter four and five. The work presented in this thesis has not yet been published but is in preparation.
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Chapter 1

Introduction

In the early 1930’s, sulfonamides became a very important class of antibiotics, now known as sulfa drugs. The first of these antibiotics was the dye prontosil, Figure 1.1; the discovery of its antibacterial effect was revolutionary⁶ and earned Gerhard Domagk the 1939 Nobel prize in physiology or medicine.⁷ Prontosil went on to save many lives, and an account in 1936 at Vancouver General Hospital⁸ recounts a trial of a young girl with streptococcal meningitis,

“December 22nd — The patient was very irritable and objected to being moved. Stiffness of the neck was pronounced. Kernig’s test was very definitive. ”

After the administration of intravenous prontosil,

“December 25th— The patient was very much improved....She felt so well that she sat up and ate a small Christmas dinner of turkey.”⁸

The active portion of prontosil was found to be sulfanilamide.⁹ The biological effect of prontosil is generated by competition for p-aminobenzoic acid which is involved in the synthesis of folate in bacterial cells, but not in human cells, where it is acquired by diet.¹⁰,¹¹

Today, sulfonamides are found as integral parts of antiviral and anticancer drugs like Novartis’s LG8X18 (Encorafenib)¹² which is an enzyme inhibitor for
the treatment of melanoma. Others, like acetazolamide (Diamox)\textsuperscript{13} and brinzolamide (Azopt),\textsuperscript{14} are carbonic anhydrase inhibitors,\textsuperscript{15,16} used in the treatment of epileptic seizures, glaucoma, and macular edema. Sulfonamides are also found in COX-2 inhibitors\textsuperscript{17} which are used as anti-inflammatory drugs. The sulfonamide moiety can impart properties not achieved with other functional groups, like sulfonyls or carboxamides. For example, the many faceted celeboxib, known on the market as Celebrex, is both a COX-2 and carbonic anhydrase (CA) inhibitor;\textsuperscript{3,18} an analogous COX-2 inhibitor, the drug rofecoxib (Vioxx), has a methyl sulfone moiety instead,\textsuperscript{3} and cannot confer CA inhibition, \textbf{Figure 1.2}.

The ability to manipulate the sulfur-nitrogen bond in sulfonamides are critical in the release of NO and/or HNO. Studies have shown NO and/or HNO is released by compounds like Angeli's Salt (Na\textsubscript{2}N\textsubscript{2}O\textsubscript{3}), acyl nitroso containing compounds RCONO,\textsuperscript{19} and—more importantly to this thesis—sulfur-nitrogen bond containing compounds such as S-nitrosothiols RSNO\textsuperscript{20} and sulfonamides. Nitric oxide (NO) is a known signaling molecule involved in biochemical, cell biological and physiological processes. Robert F. Furchgott, Ferid Murad and Louis Ignarro earned the Nobel Prize in Physiology or Medicine in 1998 for their independent study of the metabolic pathway of nitric oxide in smooth muscle vasodilation.\textsuperscript{21–24} Fukuto and colleagues have reported the closely related azanone (HNO) to also elicit vasorelaxation \textit{in vivo}.\textsuperscript{25} While very similar, NO and HNO have distinct biochemical pathways of inducing activity in the body; HNO induces venous vasodilation, whereas NO results in arterial vasodila-
Figure 1.2: A pairing of COX-2 inhibitor drugs, celecoxib, Celebrex and rofecoxib, Vioxx. Note that rofecoxib lacks a sulfonamide functional group.

It has been shown by Miranda et al. that HNO has a longer oxidation lifetime than NO and as such would greatly influence biological effects. Bonner et al. suggest that N-hydroxy benzenesulfonamide, also known as Piloty’s acid, can release HNO and it has been subsequently shown that N-hydroxy benzenesulfonamide derivatives will release azanone at physiological pHs. Sulfonamides are also advantageous in that its pharmacological effects can be modified via structural changes to the sulfonamide moiety. Commonly used NO/HNO releasing drugs (either directly or via an NO/HNO cascade) are the anti-migraine sumatriptan (Imitrex), the anti-hypertensive Indapamide (Lozol) and the popular muscle relaxer sildenafil (Viagra).

Yet, while we know these molecules play roles in these important processes, what their reactivities are and how they elicit biological responses remains unclear. As a functional group, sulfonamide reactivities have been shown to be very different from structurally similar functional groups. For example, they are much less electron-withdrawing than their corresponding sulfonate esters, carbonyls or amides. The N–H acidities of sulfonamides, pKₐ 8, are higher
than corresponding amides, pKᵢ 15, but C—H acidities are lower than carbonyls which can make them quite favorable for use in synthesis as protecting groups due to the ease of deprotonation in mildly basic environments.¹⁰

Transmission effects through the sulfur-nitrogen bond have long been of interest and have been studied using a variety of techniques. The nature of the sulfur-nitrogen bond and its σ and/or π character has been much debated. For example, Raban et al. have shown, using NMR, that sulfenamides (RSNH₂) have large rotational barriers which are attributed to nitrogen-sulfur p-d π bonding. As the sulfur undergoes oxidation to sulfinamide and then to sulfonamide the rotational barrier energy decreases, decreasing the sulfur-nitrogen π character.³⁴ Yet, according to Lyapkalo et al., N,N-diisopropylhexafluorobutane-1-sulfonamide does exhibit a substantial rotational barrier.³⁵ This is attributed to appreciable sulfur-nitrogen double bond character via pπ—dπ bonding due to the electron-withdrawing effect of the perfluorobutyl substituent. Similarly, Crich and colleagues also found evidence for a rotational barrier in the SN bond in substituted hexahydropyrrolo indoles, where an electron donating substituent will reduce this barrier and electron withdrawing groups will increase the it, increasing the sulfur-nitrogen π bond character.³⁶

Other studies have debated the role of sulfur d orbitals and its affect on transmission through the sulfur-nitrogen bond. NMR studies of arylsulfonamides have indicated little conjugation involving the arylsulfonamide sulfur d orbitals and the phenyl p orbitals when an electron donating substituent is present, but larger overlap between the sulfur-nitrogen (pπ—dπ).³⁷ However, Reed et al. have shown that SN π bonding occurs not through the involvement of sulfur d-orbitals but through negative hyperconjugation in 32-valence-electron-species of X₃AY (O₃ClF, F₃SN, CF₄, etc.)³⁸ This is further supported by sulfur K-edge XAS data and computational work on sulfonyl chlorides which describes hyperconjugation via mixing of the aryl π-system into the SClπ⁺ orbital.³⁹

The complex and puzzling nature of the sulfonamide molecule continues in the measured dipole moments of sulfonamides, which are larger than theoretical calculations would suggest.⁴⁰ This has been interpreted as evidence that greater separation of charge will contribute to the stability of the molecule.⁴⁰ Electron-donating phenyl groups were shown to stabilize the sulfonamide more
than electron-withdrawing groups by forming a C=S resonance structure with a positive sulfonamide sulfur and a weakened S−N. Conversely, electron-withdrawing groups strengthen the S−N bond and can form a S=N double bond. X-ray crystallography supports this with a trend of S−N bond lengths increasing with electron donating R-groups. Again, these data further suggest that modifications of the sulfonamide moiety can manipulate the sulfur-nitrogen bond which can be directed toward drug design.

Studies on related S−N containing molecules, S-nitrosothiols (RSNO), have provided interesting insight on the nature of the sulfur-nitrogen bond. X-ray absorption spectroscopy (XAS) of primary and tertiary RSNOs have been shown to exhibit sulfur-nitrogen π* contribution. In the spectra of these primary and tertiary RNSOs, Figure 1.3, the low energy shoulder has been assigned to the S1s to SNπ* which is supported by DFT simulations. Significant electron donation from R-groups in tertiary RSNOs lead to a lowering of Z_eff while the opposite is true in primary RSNOs. This is further bolstered by theoretical work done by Timerghazin et al. where a S=N resonance structure is shown to play an important role in the stabilization of RSNOs. Herein, similar methods will be applied to investigate the stability of the sulfur-nitrogen bond in sulfonamides, which may orchestrate NO/HNO release.

In this thesis, a systematic study of the sulfur-nitrogen bond within sulfonamides is undertaken so as to understand how the electronic distribution of sulfinated amides will affect the nature and strength of this bond; particular focus on the nature of the sulfur-nitrogen bond is important for both the release of azanone as well as structural modifications to the sulfonamide moiety and its ramifications on functionality in enzyme inhibition. In Chapter two, an overview of x-ray absorption spectroscopy, sulfur K-edge spectroscopy and density functional theory is given. Chapter three introduces systematic modifications to the sulfonamide moiety through the addition of oxygen to the sulfur atom and modifications to the R-group, and how these effect the sulfur-nitrogen bond. In Chapter four, the synthesis of a range of Hammett para-substituted N-hydroxy sulfonamides is discussed and compared to the parent sulfonamide via structure-function relationships using NMR, IR, crystallography and XAS. The contribution of the electron-withdrawing and electron-donating nature per
(a) S K-edge spectra of (A) S-nitroso-glutathione (dashed), (B) S-nitroso-N-acetylpenicillamine (solid), (C) trityl thionitrite (dotted), and (D) second derivative of XAS spectra.

(b) TD-DFT calculation of S-nitrosothiol, ethyl-S-nitrosothiol.

Figure 1.3: Sulfur K-edge XAS data and computational simulation of sulfur-nitrogen $\pi^*$ character in S-nitrosothiols. reprinted with permission from.\textsuperscript{4} Copyright 2008 Canadian Science Publishing or its licensors.
substituent to the overall electronic structure is discussed. Chapter five further delves into a detailed computational assessment and assignment of the XAS transitions for the sulfonamide compounds studied in Chapter four. Finally, Chapter six summarizes the findings of this thesis and future directions are discussed.
Chapter 2

X-Ray Absorption Spectroscopy and Density Functional Theory

2.1 X-Ray Absorption Spectroscopy (XAS)

When an x-ray of energy equal to or greater than the binding energy of a core electron is absorbed by an atom, that electron is excited. This excitation promotes the ejection of an electron with the energy of the incoming photon minus the electron-binding energy:

\[ E_{\text{excited}} = h \omega - E_{\text{core}} \]

(2.1)

where \( \omega \) is the incoming photon’s energy and \( E_{\text{core}} \) the binding energy of excited core level. The ejected electron, in turn, creates a core hole, which is filled by the relaxation of outer shell electrons. This relaxation can occur radiatively or non-radiatively, Figure Figure 2.1, releasing a photon or an electron, respectively. The shell and subshell from which the excited electron originates lends its name to the edge: K edge = 1s; \( L_1 \) edge = 2s, \( L_2 \) edge = \( 2p_{1/2} \), \( L_3 \) = \( 2p_{3/2} \), et cetera. The energy of the ejected core electron is characteristic of the emitting atom. As a result, XAS is an element specific technique, with
well defined binding energies for neighboring atoms. For example, the sulfur 1s binding energy is 2472 eV, phosphorous 1s is 2145.5 eV and chlorine 1s is 2822.4 eV. \[46\]

**Figure 2.1:** The incoming photon creates a core hole as the core electron is ejected from the 1s orbital. An Auger electron or a fluorescent photon is emitted upon relaxation to fill the core hole by outer shell electrons.

X-ray absorption spectroscopy (XAS) involves the excitation of core electrons into empty (or partially-empty) bound electronic states, or ionized into the continuum as shown in Figure 2.2. The XAS spectrum contains a large absorption called the ‘edge jump’, or ‘white line’, which denotes the ionization of the core electron to the continuum.

The generated XAS spectrum may be split into two regions: the x-ray ab-
Figure 2.2: Bound transitions to empty and partially empty MOs can be seen in the pre-edge and shoulder while transitions to the continuum can be seen in edge jump.

sorption near-edge structure (XANES) and the extended fine structure (EXAFS). The near-edge region begins several eV below the edge jump to 30-50eV past it, while, EXAFS begins at the end of the XANES region to well past the white line.\textsuperscript{47,48} The near edge region arises from bound transitions which are dominated by electric dipole allowed transitions of $\Delta \ell = \pm 1$ (where $\ell$ is the orbital quantum number) to vacant antibonding molecular orbitals with p character, $1s\leftarrow np$.\textsuperscript{49,50} As the XAS spectrum reflects atoms directly involved in bonding interactions, the XANES region is very sensitive to oxidation states and geometries and is a direct probe of covalency.\textsuperscript{51–53} The intensity of the
transition is dependent on the probability of the transition from the initial state to the final state based on Fermi’s golden rule.\textsuperscript{54}

At energies above the edge are oscillatory structures that correspond to the EXAFS. Here, the electron now possesses kinetic energy above the ionization threshold and can interact with its nearest neighbor atoms. These scattering interactions lead to constructive and deconstructive interference which correlates to the local geometry of the absorbing atom and can be used to determine interatomic distances and coordination numbers.\textsuperscript{55,56}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{xray_absoption_spectrum.png}
\caption{X-ray absorption spectrum, shown are the main absorption peak with a shoulder and the XANES and EXAFS regions.}
\end{figure}

Detection of the XAS signal is often achieved in transmission mode. The intensity of the incoming beam is measured before ($I_0$) and after ($I$) the sample, as per equation 2.2.

$$\text{Transmittance} = \left( \frac{I}{I_0} \right)$$

(2.2)

The absorbance is dependent on the concentration ($c$), the molar absorptivity ($\epsilon$) and pathlength ($b$) in accordance with Beer’s Law, $A = \epsilon bc$. In the case of a solid sample, as is commonly used at beamlines, the sample thickness ($x$) is
used in place of pathlength, as in equation 2.3.

\[ I = I_0 e^{-\mu x} \] (2.3)

Fluorescence detection is also utilized, commonly concurrently with transmission detection. The cross-section of fluorescence emission is proportional to the absorbance. Fluorescence detection can, however, experience saturation of the signal if the sample is not dilute as all incoming x-rays that interact with the sample can contribute to the fluorescence signal. If the sample is too concentrated or thick, signal saturation or self-absorption will occur. This self-absorption will decrease and distort signal intensities.\(^{47}\) Total electron yield detection (TEY) can also be used in conjunction with fluorescence. TEY detects all emitted Auger and secondary electrons and has a shallow penetration depth which allows for surface analysis and in turn is not susceptible to self-absorption due to thick samples.\(^{56,57}\) In this thesis both fluorescence and TEY XAS data were collected.

![Experimental setup for transmission and fluorescence signal detection.](image)

**Figure 2.4:** Experimental setup for transmission and fluorescence signal detection.
2.1.1 Sulfur K-Edge X-Ray Absorption Near Edge Structure (XANES)

XANES is a particularly useful technique in the study of sulfur containing compounds. Sulfur can be a difficult element to study spectroscopically which has lead to its characterization as a ‘spectroscopically silent’ element. Insight via NMR is insufficient due to the absence of $^{32}$S nuclear spin; and the use of $^{33}$S is curbed by the expense along with the weak and broad signals obtained. This also means that compounds must be modified and cannot be tested in situ. EPR can also be very useful but only when the sulfur species has an unpaired electron.

S K-edge XAS permits a unique perspective of bonding from the viewpoint of the sulfur atom; as absorption occurs from the S $1_s$ core orbital to electric dipole-allowed bound transitions to np molecular orbitals. These are antibonding molecular orbitals which are localized around the sulfur and have substantial sulfur 3p character. As these MOs are directly involved in bonding interactions, S K-edge XAS reflects sulfur bonding, and as such are sensitive to oxidation states and geometries. The sulfur K-edge XAS is advantageous due to its large span in chemical shift through a range of sulfur oxidation states, Figure 2.5.

It has been shown through metal-ligand XAS using metal tetrathiolates that pre-edges are a direct probe of sulfur covalency. Since the transitions from $S1_s$ are localized on the ligand, in this case a thiolate, absorption intensity can only occur if the receiving MO has substantial sulfur 3p character. This ligand 3p character, hence, is the result of covalency. As per Hedman et al.:

$$I(S1s \rightarrow \psi^*) = \alpha^2 I(S1s \rightarrow 3p)$$  \hspace{1cm} (2.4)

Where $I$ is the intensity of the transition, $\psi^*$ the transition from 1s to np orbital and $\alpha^2$ represents the amount of sulfur 3p character in the MO.

The uncertainty in the pre-edge features are limited by the instrumental resolution of approximately 0.1eV. The spectra also exhibit relatively sharp linewidths due to the longer core-hole lifetime of the sulfur 1s excitation energy, $\Delta E \Delta t = (\frac{1}{2}) \hbar$. S K-edge XAS is also an excellent tool for in situ use, as
Figure 2.5: Oxidation state changes of sulfur in methionine, reprinted with permission from.\textsuperscript{5} Copyright 2009 ACS.

2.1.2 Experimental Setup
Sulfur K-edge XAS data were acquired at both Stanford Synchrotron Radiation Lightsource (SSRL) and Canadian Light Source (CLS). Fluorescence data were collected at beamline 4-3 at the Stanford Synchrotron Radiation Lightsource (SSRL) under ring conditions of 3 GeV and 200-500 mA. Solid samples were ground finely with 50% boron nitride, to minimize self-absorption, and mounted as a thin layer on sulfur-free Kapton tape at room temperature. Fluorescence data were acquired using solid state detector at ambient temperature and pressure. Energy calibration was carried out using sodium thiosulfate (Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3}) with the first pre-edge feature being calibrated at 2472.02 eV.\textsuperscript{59} Resolution of incoming beam was approximately 0.1 eV. Total electron yield data were acquired at beamline SXRMB at the CLS under ring conditions of 3 GeV and 180-250 mA. Solid samples were ground finely with 50% boron nitride and mounted onto a copper sample holder with carbon tape. Total electron yield data were acquired under vacuum at ambient temperature. Calibrations were performed as above.
2.1.3 Data Analysis

Raw data were normalized to incoming beam (Io), calibrated to the first thiosulfate peak and scans averaged with the Matlab program BlueprintXAS\textsuperscript{60} pre-fit function. Due to sulfur photo-reduction in the fluorescence data, only the first scans of each run were used for tertbutanesulfinamide and potassium dinitrososulfite in Chapter 3. As TEY does not exhibit such photo-reduction, all scans per run of the rest of the sulfonamide compounds in this thesis were averaged for greater signal-to-noise ratio. Background subtraction and normalization (where the pre-edge slope is equated to zero and the post-edge to 1) of the spectra were achieved using BlueprintXAS.\textsuperscript{61} For background subtraction and normalization a pre-edge and post-edge slope were estimated and pseudo-Voight peak components added until all peaks in the spectra were represented. Model selection employing the Akaike information criterion (AIC)\textsuperscript{62,63} was used to estimate the optimum number of peaks needed to fit the spectrum properly. The model, for example a 3-peak model versus a 4-peak model, with the lowest AIC was chosen for fitting all spectra. Each parameter input by the user is bound by upper and lower limits; fits were achieved via Monte Carlo based search, chosen from the bounds provided by the user. Fits with smallest sum of squared errors were chosen for background subtraction and normalization which lead to the data shown in this thesis. Energies reported in this thesis were determined from the inflection point of the first derivative of the spectrum in question.

2.2 Density Functional Theory

Density functional theory (DFT) is commonly used in conjunction with XAS to describe and model the spectra that are acquired during experimentation. DFT is based on the electron probability density function of a molecule, replacing the wavefunction based methods of Hartree-Fock and ab initio calculations. The electron density of a molecule is a function only of its position, \( \rho(x, y, z) \). Unlike the wavefunction, electron density is an experimental observable which
can be measured with methods like x-ray diffraction or x-ray fluorescence.\textsuperscript{64,65}

DFT stems from Hohenberg and Kohn’s two theorems.\textsuperscript{66} The first theorem states that the ground state electron density $\rho(x, y, z)$ determines all ground-state properties.\textsuperscript{67} Any ground state property is a functional of the of this electron density function; for example the energy would be given as $E_o = F[\rho_o] = E[\rho_o]$.\textsuperscript{64}

The second theorem states that the functional $F[\rho_o]$ will yield the lowest energy if and only if the density used is the true ground state electron density. This is DFT equivalent of the wavefunction variation theorem and puts an upper boundary on the true energy.

The theorems of Hohenberg and Kohn do not go on to explain how to find the functional $F[\rho_o]$. Kohn and Sham however, proceed to give us a procedure whereupon the known quantities can be found with explicit functions and the functional can be approximated. In the Kohn-Sham equations, the electronic energy of the molecule is separated into a portion which can be calculated accurately without DFT plus a small term which contains the functional.\textsuperscript{64} The first term of equation 2.5 integrates the potential energy of each nucleus and $\rho_o$; the second, the non-interacting electrons’ kinetic energy; the third term the electrostatic repulsion. The only unknown is the electron-electron interactions; the functional of $F[\rho_o]$, which is conveniently combined into the final term.

\[
E_0 = -\sum_A Z_A \int \frac{\rho_o(r_1)}{r_{1A}} dr_1 \\
- \frac{1}{2} \sum_{i=1}^{2n} \langle \psi_{1}^{KS} (1) | \nabla_{1}^{2} | \psi_{1}^{KS} (1) \rangle \\
+ \frac{1}{2} \int \int \frac{\rho_o(r_1)\rho_o(r_2)}{r_{12}} dr_1 dr_2 \\
+ E_{XC}[\rho_o]
\] (2.5)

This equation is exact, so if $\rho_o(r_1)$ and the exchange-correlation were known, the exact energy would be found. Since this currently cannot be achieved, approximations are used to improve this exchange-correlation.\textsuperscript{64} One is the local
density approximation (LDA), in which a uniform electron gas is used a model. Another is the generalized gradient approximation (GGA) which adds the gradient of the charge density to the LDA. Hybrid functionals, a newer approach, add Hartree-Fock exchange to the $E_{XC}[\rho_0]$ term of the energy equation.

Basis sets are used to describe atomic orbitals and, by extension, molecular orbitals. A basis set is the linear combination of atomic orbitals to approximate molecular orbitals. The simplest basis sets consist of only $p$ atomic orbitals, like the simple Hückel basis set. Other basis sets can add polarization functions, allowing the electron density to distort from its ideal symmetry, or diffuse functions allowing orbitals to extend in space. There are a variety of basis sets that can be used depending on the molecular system and computational time frame needed.

### 2.2.1 Theoretical Simulations of XAS Data

DFT is to use to simulate and model the XAS spectrum of a molecule. XAS spectra are excited state spectra and DFT are ground state calculations, so we must find a way to describe the excited state. This is done by adopting time-dependent density functional theory (TD-DFT) to yield the transition energy instead of the excited state energy. According to DeBeer and Neese, "one solves the time-dependent linear response equations in the subspace of particle-hole pairs that only correspond to excitations from the sulfur 1s-core orbitals into the empty valence spin-orbitals." This procedure yields error in the absolute energies, but the relative energies are reproducible and systematic. Shifting the calculated spectrum a set number of electron-volts, which is dependent on the functional used, leads to proper alignment with experimental data; for example BP86 calculated spectra are shifted +76 eV while B3LYP are shifted by 55eV.

All calculations within this thesis were performed using the ORCA quantum chemistry program. DFT calculations were run with spin-unrestricted Kohn-Sham equations. A variety of functionals and basis were used and will be stated in detail in the following chapters. Relativistic effects (ZORA) were not employed as the sulfur atom is not a particularly heavy atom and the inclusion of
ZORA did not alter the spectra while requiring more computational time. Geometry optimizations were performed and vibrational frequency calculations were attained using NUMFREQ. Fully optimized geometries showed only positive frequencies indicating a local minimum was obtained. Single point calculations for the excited state spectra were implemented using XES excitation from the sulfur core orbital.
Chapter 3

The Effect of Oxidation on Sulfur-Nitrogen Molecules

3.1 Introduction

The sulfonamide moiety has been an important motif in many biologically active compounds and plays a key role in the efficacy of sulfa drugs. Sulfonamides are also found in vivo where they can act as enzyme inhibitors and are also used in organic synthesis as chiral building blocks and protecting groups. As shown in the introduction, previous work on thioethers and S-nitrosothiols demonstrate that XAS can be a useful tool for the exploration of sulfur containing compounds. Sulfonamides, which consist of similar structural aspects to thioethers and S-nitrosothiols, will undergo analogous XAS analysis and comparison to DFT calculations.

In this chapter, systematic modifications to the R-group and changes to the oxidation states of the sulfur atom will afford a chance at characterizing this framework, R–S(O)n–NH₂, see Scheme Scheme 3.1. Three oxidation states of methyl, benzyl and tert-butyl sulfonated amides will be studied: methanesulfenamide (1e), methanesulfinamide (1i), methanesulfonamide (1o); tertbutanesulfenamide (2e), tertbutanesulfinamide (2i), tertbutanesulfonamide (2o); ben-
zenesulfenamide (3e), benzenesulfinamide (3i), benzenesulfonamide (3o).\textsuperscript{1} Potassium dinitrososulfite (4x) is used as a representative for a sulfinate compound.

\begin{align*}
\text{H}_3\text{C} - \text{S} - \text{NH}_2 & \rightarrow \text{H}_2\text{C} - \text{S} - \text{NH}_2 & \rightarrow & \text{H}_3\text{C} - \text{SO} - \text{NH}_2 \\
\text{S} - \text{NH}_2 & \rightarrow & \text{SO} - \text{NH}_2 \\
\text{S} - \text{NH}_2 & \rightarrow & \text{SO} - \text{NH}_2 \\
\end{align*}

\textbf{Scheme 3.1:} A library of sulfinated amides

Due to the complexity involved in the study of sulfonamides, which include stability and reactivity, a systematic approach to the dissection of the sulfonamide scaffold using DFT will be undertaken. Beginning with the zero oxygen system— sulfenamides $\text{R-S-NH}_2$— we will directly compare the effects of changing a primary alkyl to a tertiary alkyl to an aryl group. Then, we will oxidize each sulfenamide to form the sulfinamides $\text{R-SO-NH}_2$ and finally we will observe the changes affected by the second oxidation to form the respective sulfonamides $\text{R-S(O)}_2-NH_2$.

\textsuperscript{1}The designations of e, i and o come from the conventional naming of the various sulfonamide oxidation states: e for zero oxygens, i for one oxygen, and o for two.
3.2 Results and Discussion

3.2.1 XAS

Four representative compounds were selected for XAS analysis due to stability and availability: tertbutanesulfinamide (2i), methanesulfonamide (1o), benzenesulfonamide (3o) and potassium dinitrososulfite (4x), Scheme Scheme 3.2. Structurally, the representative molecules used for XAS studies are very similar. By making small systematic modifications we can track which, if any, of these changes affect the absorption spectrum and, hence, the electronic structure of these compounds.

The S K-edge XAS spectra of the sulfinated amides are shown in Figure Figure 3.1. The spectra exhibit shifts in energy consistent with changes in oxidation state. All four spectra show similarities in their overall shapes, the main feature being a single large absorption band. Both 3o and 4x have an added feature; 3o displays a prominent shoulder and 4x an additional peak.

Scheme 3.2: Representative compounds selected for XAS analysis.
The main absorption peak of 2i is found at 2477 eV; 1o at 2481.1 eV; and 3o at 2481.4 eV and with a shoulder at 2479.4 eV. Compound 4x has two peaks found at 2480.5 eV and 2482.5 eV. The difference in energy between the two sulfonamides, 1o and 3o, is 0.3 eV; a large change in energy would not be expected for two molecules with similar effective nuclear charge ($Z_{\text{eff}}$).

The energy difference between 2i and 1o/3o is 4.1 eV, whereas; for 1o/3o versus 4x, the difference is 1 eV. The chemical shifts which occur upon oxidation directly reflect the $Z_{\text{eff}}$ of sulfur; 2i has the least positive core while 4x has the most positive, indicating more delocalization of the S electron density.\(^{50}\)

The pre-edge intensities of ligand-metal XAS spectra correlate to covalency.\(^{58}\) A small caveat to mention, however, is the self-absorption that has likely occurred in the acquisition of the fluorescence data for 2i and 4x. 1o and 3o were acquired via TEY, a process which is not as susceptible to self-absorption, as stated in Chapter two. As such the intensities of 2i and 4x may not be directly comparable to one another nor to the sulfonamides 1o and 3o, hence, covalency calculations will not be carried out. Be that as it may, the spectra do reflect increased area-under-the-curve-intensities as the molecules are oxidized due to the creation of more core holes. The increase of the XAS intensity also reflects a decrease in electron density in the sulfur atom.

As modifications between each compound are small, minimal differences in the XAS spectra of the compounds are expected, as seen in Figure 3.1. Only upon substitution of an alkyl R-group with an aryl substituent do we see a new feature. It has been shown previously\(^{39}\) that this feature is characteristic of an aryl group bonded to a sulfone. It stands to reason, then, that the shoulder is due to a $S_{15}$ to $SC_{\pi}^*$ transition. Work from Martin-Diaconescu et al. and Karunakaran-Datt et al.\(^{4,5,42}\) suggest the main absorption peak is due to transitions from the $S_{15}$ to $SC_{\pi}^*$ and $S_{15}$ to $SO_{\sigma}^*$. Compounds 2i, 1o and 3o are then dominated by the $\sigma^*$ acceptor states for the S—O and S—C bond. Further assignments of features are carried out below in conjunction with DFT calculations and XAS simulations.
Figure 3.1: The S k-edge XAS spectra of tertbutanesulfinamide (2i), methanesulfonamide (1o), benzenesulfonamide (3o) and potassium dinitrososulfite (4x). a) Calibrated and normalized spectra. b) First derivative of all respective spectra.
3.2.2 DFT

All gas phase DFT calculations were run using ORCA, version 2.9.0, using the BP86 functional and TZVP basis set. No relativistic effects were added. Excited state calculations and XAS simulations were conducted with TDDFT and XES. The energies calculated for XAS simulations are shifted by +76 eV to match with the experimental spectra.68

![Figure 3.2](image.png)

**Figure 3.2:** Sulfur K-edge XAS spectrum of methanesulfonamide (1o) with simulated S K-edge XAS spectrum overlaid in dotted line. The MOs are found along the x-axis as sticks.

Comparison of the simulated and experimental XAS spectra of methanesulfonamide in Figure 3.2 are in good agreement; the molecular orbitals—shown along the bottom as sticks, define the overall shape. The MOs that contribute the most to this shape are the LUMO through LUMO+4. As the XAS spectrum is the visualization of the empty molecular orbitals we will focus on these unoccupied molecular orbitals. By using the energy density diagrams as shown in
Figure 3.3 and percent contributions we can gain insight into the electronic structure. The energy level diagram of methanesulfonamide reveals that the LUMO is a sulfur-nitrogen, interaction with some sulfur-carbon. The calculated Kohn-Sham LUMO indicates a highly delocalized molecular orbital with 12% S$_{3s}$ and 3.8% S$_{3p}$ character. Contributions from the amide nitrogen have 10.8% N$_{2s}$ character and 6.6% N$_{2p}$. The methyl carbon contributes 5.1% C$_{2s}$ character with 6.1% C$_{3p}$ character. LUMO+1 is predominately sulfur-oxygen, with 31% S$_{3p}$ character (shared, in varying amounts amongst all surrounding atoms) and 14.5% O$_{2p}$ character between the two oxygens. LUMO+2 is largely sulfur-carbon, 15.7% S$_{3s}$ character and 21.6% C$_{2p}$ character. In LUMO+3 the electron density on the central sulfur atom is equally distributed amongst all four bonds in a SC$_{\sigma}$ type interaction. LUMO+4 is a sulfur-nitrogen, the only MO with $\pi$ character that contributes to the shape of the spectrum. Overall, the first five MOs indicate that, for methanesulfonamide, bonding within the structure is based on a sigma bond framework, with a fairly electronically delocalized sulfur. Bonding to the sulfur is dominated by sigma contributions with only small S-N$_{\pi}$ contributions.

Calculations of all the oxidations states of methane sulfinated amide show shifts consistent with the changes in the core charge of sulfur, Figure 3.4, methanesulfenamide (1e) having the least positively charged core and 1o having the most. As the 1e sulfur is bonded to fewer atoms, it has fewer empty core-holes and thus less intensity in the spectrum. The MOs that contribute most to 1e are the LUMO (SN$_{\sigma}$) and LUMO+1 (SC$_{\sigma}$). Turning to 1i, the LUMO represents SN$_{\sigma}$, LUMO+1 SO$_{\sigma}$ and SC$_{\sigma}$, LUMO+2 is equally SN$_{\sigma}$ and SC$_{\sigma}$ and LUMO+3 SC$_{\sigma}$ and SO$_{\sigma}$. The MOs that contribute most to the shape of the 1i spectrum are LUMO+2 (SN$_{\sigma}$ and SC$_{\sigma}$) and LUMO+3 (SC and SO$_{\sigma}$). 1o has been discussed above, where LUMO+1 (SO$_{\sigma}$) and LUMO+3 (SCON$_{\sigma}$) are the main contributors to the peak shape. The two peaks in 1e merge closer to one another with each addition of oxygen until in 1o there only a single peak. This suggests that the addition of oxygen increases mixing of the electron density of sulfur demonstrated by the decrease in splitting of the sulfur-nitrogen, MOs and the sulfur-carbon, MOs as evidenced by the decrease in the energy differences between those MOs.
Figure 3.3: a) Simulated XAS spectrum with MO assignments for the first five MOs. b) Energy level diagram of methanesulfonamide with assignments and energy density diagrams.
The calculated bond lengths of the sulfur-carbon bond vary with each addition of oxygen. 1e has a S-C bond length of 1.832 Å; 1i, 1.850 Å; and 1o, 1.817 Å. For the sulfur-nitrogen bond 1e has a bond length of 1.755 Å; 1i, 1.763 Å; and 1o is 1.730 Å. The SC and SN both are longest for the sulfinamide and shortest for the sulfonamide.

The experimental XAS and simulated spectrum, seen in Figure 3.5 of tertbutanesulfinamide also show good agreement, the slight misalignment being due to the +76eV shift used to maintain consistency between all calculations. The molecular orbitals that contribute most to the XAS spectrum are the LUMO and LUMO+1 with some LUMO+3. LUMO is a SN σ* with SO π*, 33% S 3p, 15.5% N 2p and N 2s and 10.3% O 2p character combined. LUMO+1 and LUMO+3 are combination SC σ* with SO π*. LUMO+1 has 36.1% S 3p, 11.5% C 2p and 7.7% O 2p. LUMO+3 has 21.6% S 3p, 9.9% C 2p and 12.2% O 2p. This MO scheme, as seen in Figure 3.5, is similar to that of 1o, with lower energy MOs being centered around the sulfur-nitrogen σ* transition and the higher energy MOs with sulfur-carbon σ* transitions.

The DFT calculations for all the oxidation states of tertbutanesulfinamide, are similar to those of methanesulfonamide and its variants, with the exception of some changes in energies. As a drastic change in R-group has not occurred, drastic changes in the XAS are not be expected. As the sulfur atom is oxygenated the energy splitting decreases in the MOs for SNσ*, SOπ* and SCσ* so that the features become unresolved in the XAS spectrum. Again, the oxygen additions encourage mixing of the electron density of sulfur amongst its neighbors.

A look at the bond lengths show that for the sulfur-carbon bond, 2e has a bond length of 1.885 Å; 2i, 1.927 Å; and 2o, 1.889 Å. For the sulfur-nitrogen bond the bond distances are as follow: 2e, 1.752 Å; 2i 1.764 Å; and 1.737 Å. Similar to the methyl substituent, the SC and SN is longest for the sulfinamide, but the SC is shortest for 2e and the SN is shortest for 2o. This may be due to the fact that the t-butyl group is more electron donating than the methyl group and the contraction of the SN bond is an inductive effect mitigated by the two electron-withdrawing oxygens.

The XAS simulation of benzenesulfonamide is shown in Figure 3.7.
Figure 3.4: Methane sulfinated amides, a) Simulated S K-edge XAS spectra of 1e, 1i and 1o. b) Energy level diagram of the three oxidation states of methane sulfinated amide.
Figure 3.5: Tertbutanesulfinamide (2i) XAS spectrum and simulated XAS spectrum overlaid in dotted line with assignments for the first four MOs. The star indicates a feature in the experimental data which has not yet been explained.

Here, we clearly see the shoulder of the experimental spectrum is predicted in the simulation. While the intensity and absolute energy are not exactly reproduced, the overall shape is consistent. The addition of the phenyl group clearly has a large impact on the sulfur-carbon bond, which is absent in the alkyl group substituents.

The immediately noticeable feature is the LUMO (and to a much smaller extent LUMO+1) which make up the shoulder in the spectrum. LUMO is a $\pi^*$ with the phenyl ring in a $\Phi_5$ configuration. LUMO+1 has no sulfur contribution, the electron density being confined at the $\Phi_4$ of the phenyl group. The first difference between the aryl and alkyl substituents is this $\pi$ system that is introduced.
Figure 3.6: tert-Butyl sulfinated amides, a) Simulated S K-edge XAS spectra of 2e, 2i and 2o. b) Energy level diagram of the three oxidation states of tert-butyl sulfinated amide.
Figure 3.7: Sulfur K-edge XAS spectrum of benzenesulfonamide (3o) with simulated S K-edge XAS spectrum overlaid in dotted line. The first seven MOs are found along the bottom as sticks.

The greatest contributors to the main absorption peak of 3o are LUMO+2 through LUMO+5. LUMO+2 exhibits a delocalized sulfur, framework with all four of the neighboring atoms. LUMO+3 and LUMO+4 are SN, and SO. The breakdown of the XAS spectrum differs from the previous alkyl sulfonated amides in that the SN moves higher in energy while the SC moves to lower MO energies.

The comparison of all the oxidation states of benzenesulfonamide begins to show major differences to the previous two compounds. For 3e, the LUMO is the phenyl ring in a configuration with no sulfur contribution and, hence, no contribution to the simulated XAS. LUMO+1 is SN, similar to the previous compounds. LUMO+2, however, is a SC which is so close in energy to LUMO+1 that the two are not resolved in the spectrum and contribute almost
Figure 3.8: Benzene sulfinated amides, a) Simulated S K-edge XAS spectra of 3e, 3i and 3o. b) Energy level diagram of the three oxidation states of benzene sulfinated amide.
equally to the first absorption peak. At LUMO+3 the SC$_{\sigma^+}$ transition makes up the second, higher energy, absorption peak.

Upon oxygenation, however, the LUMO for 3i is no longer a sulfur-nitrogen MO but a sulfur-carbon$_{\sigma^+}$ and a $\Phi_5$ MO. LUMO+1 is once again the $\Phi_4$ phenyl ring, with no sulfur contribution. LUMO+2 is where the SN$_{\sigma^+}$ MO is found. LUMO+3 is predominately a SO$_{\sigma^+}$ and the SC$_{\sigma^+}$ is found at LUMO+4. In 3o, as discussed above, the sulfur-carbon$_{\sigma^+}$ now becomes mixed with the SN$_{\sigma^+}$ and SO$_{\sigma^+}$. LUMO+3 and LUMO+4 are SN$_{\sigma^+}$ without any contributions from the phenyl ring to the sulfonamide moiety. The sulfur-nitrogen MOs move to higher energies than seen previously in either 3e or 3i nor in the oxidation states of 1 and 2. A ‘pure’ SC$_{\sigma^+}$, one that has an electron density diagram like that of 3e LUMO+3, is found at LUMO+6 for 3i and LUMO+7 for 3o.

The sulfur-carbon bond distances for the phenyl substituent are as follows: 3e, 1.801 Å; 3i, 1.848 Å; and 3o 1.818 Å. For the sulfur-nitrogen: 3e, 1.744 Å; 3i, 1.760 Å; and 3o, 1.726 Å. Once again, the longest bond lengths for SC and SN belong to the sulfonamide. The shortest, mirror the t-butyl substituent’s with 3e exhibiting the shortest SC and 3o the shortest SN.

For another perspective on the overall affects of substituent modifications, Figure Figure 3.10 shows all three of the sulfenamides compounds. The molecular orbitals displayed are equivalent, for example; the LUMO of 1e is the same as LUMO for 2e which is the same as LUMO+1 for 3e, as per Figure Figure 3.9. The sulfur-nitrogen$_{\pi^+}$ molecular orbitals for 1e, 2e, and 3e occur at similar energies. This is expected as no modifications to the amide have taken place; and the changes in R group manifest in a small transmission of electronic effect to the sulfur-nitrogen bond. Greater changes are expected, and seen, in the sulfur-carbon MOs with the substitutions of the different R groups. The energies of both SC$_{\sigma^+}$ and SN$_{\pi^+}$ MOs are lowest is 2e, due to the increased electron donating nature of the tert-butyl moiety onto the sulfur. This is followed by 1e then 3e, with the electron withdrawing effect of the aryl carbon increasing the $Z_{\text{eff}}$ of the sulfur atom. This order is also reflected in the predicted SC bond lengths: 2e, 1.885 Å; 1e, 1.832 Å; 3e, 1.801 Å.

Figure Figure 3.11 shows that the sulfinamides peaks begins to merge to form one peak. A similar comparison to the sulfenamides above shows agree-
ment to the sulfur-nitrogen\(\sigma^*\) energies to follow the trend of tertbutane < methane < benzene. The sulfur-carbon\(\sigma^*\) for 1i and 3i this time are much closer to one another, with 2i again at a lower energy than its methyl and phenyl counterparts. Both the sulfur-carbon and sulfur-nitrogen bond lengths also reproduce a similar trend to the MOs where 2i is the longest, followed by 1i and the shortest being 3i. An interesting feature, the intensities of the SC\(\sigma^*\) MOs are much lower than the SN\(\sigma^*\) indicating more electron density around the respective sulfur-carbon bonds. Finally, a comparison of the sulfonamides, Figure Figure 3.12 reveals that the ordering of sulfur-nitrogen MOs and the SN bond lengths are similar to those of the sulfinamides. A different ordering arises with the sulfur-carbon\(\pi^*\) MO energies 1o < 2o < 3o. This order is not reflected in the SC bond lengths.

Following from the above comparisons, sulfenamides are mostly affected by the changes in the R-group, \(R-S-NH_2\) —especially as the amide remains unchanged. For the sulfinamides, the addition of the oxygen atom overcomes the modifications in R-group and the amide becomes more important electronically, \(R-SO-NH_2\). As the oxidation of sulfur increases, increased shielding of core sulfur electrons lead to less electron density for the sulfur-nitrogen\(\sigma^*\) and sulfur-carbon\(\sigma^*\) transitions. If the R-group is aromatic then the sulfur-carbon \(\pi\) bond
becomes an element to consider in its possible resonance structure,\textsuperscript{43} which can be represented as shown in Figure Scheme 3.3a. For the sulfonamides, there is considerable delocalization of the electron density so that substitutions on either side of the sulfonyl will have an impact on the overall electronic distribution of the molecule, $\text{R-SO}_2\text{-NH}_2$. The contribution of the $\text{SN}_\sigma^*$ transitions to the simulated XAS spectral shape are smaller than the $\text{SC}_\sigma^*$ indicating the amide is less affected by this second oxygenation and that the $\text{SN}_\sigma^*$ is more electron rich. For the sulfur-carbon,$\sigma^*$ transition, the XAS intensity increases indicating a decrease in electron density as the electron withdrawing nature of the R-group increases. Again, an aromatic group will impact the resonance structure as shown in Figure Scheme 3.3b.

![Simulated XAS spectra with similar MOs represented for 1e methanesulfenamide (teal), 2e tertbutanesulfenamide (red), and 3e benzenesulfenamide (blue).](image-url)

\textbf{Figure 3.10:} Simulated XAS spectra with similar MOs represented for 1e methanesulfenamide (teal), 2e tertbutanesulfenamide (red), and 3e benzenesulfenamide (blue).
Figure 3.11: Simulated XAS spectra with similar MOs represented for 1i methanesulfinamide (teal), 2i (red) tertbutanesulfinamide, and 3i benzenesulfinamide (blue).
Figure 3.12: Simulated XAS spectra with similar MOs represented for 1o methanesulfonamide (teal), 2o tertbutanesulfonamide (red), and 3o benzenesulfonamide (blue).
Scheme 3.3: Expected resonance structures with the substitution of an aromatic R-group for sulfinated amides, a) sulfinamides and b) sulfonamides.
3.3 Experimental

3.3.1 Materials
Methanesulfonamide (98% purity) and benzenesulfonamide (≥98% purity) used in this study were purchased from Sigma-Aldrich. Methanesulfonamide: $^1$H NMR (300 MHz, DMSO) $\delta$ 2.91 (s, 3H, CH$_3$), $\delta$ 6.80 (s, 2H, NH$_2$); Benzenesulfonamide: $^1$H NMR (300 MHz, DMSO) $\delta$ 7.83 (d, 2H, $J$=6Hz), $\delta$ 7.58 (m, 3H), $\delta$ 7.35 (s, 2H). Potassium dinitrososulfite (Pelouze's Salt) and tertbutanesulfinamide (Ellman's sulfinamide) were synthesized in the laboratory of Scott Bohle at McGill University.

3.3.2 XAS Acquisition and Data Analysis
Sulfur K-edge XAS data for potassium dinitrososulfite and tertbutanesulfinamide were acquired at Stanford Synchrotron Radiation Lightsource (SSRL). Fluorescence data were collected at beamline 4-3 at the Stanford Synchrotron Radiation Lightsource (SSRL) under ring conditions of 3 GeV and 200-500 mA. Solid samples were mixed 1:1 with boron nitride, finely ground, to minimize self-absorption, and mounted as a thin layer on sulfur-free Kapton tape at room temperature. Fluorescence data were acquired using solid state detector at ambient temperature and pressure. Energy calibration was carried out using sodium thiosulfate (Na$_2$S$_2$O$_3$) with the first pre-edge feature being calibrated at 2472.02 eV.\(^59\)

Sulfur K-edge XAS data for methanesulfonamide and benzenesulfonamide were acquired at the Canadian Light Source. Total electron yield data were acquired at beamline SXRMB at the CLS under ring conditions of 3 GeV and 180-250 mA. Solid samples were mixed 1:1 with boron nitride, finely ground and mounted onto a copper sample holder with carbon tape. Total electron yield data were acquired under vacuum at ambient temperature. Calibrations were performed as above.

Raw data were normalized to incoming beam ($I_0$), calibrated and averaged with the BlueprintXAS \(^60\) prefit function. Only the first scans of tertbutanesulfinamide and potassium dinitrososulfite were used due to sulfur photo-reduction.
in the fluorescence data. As TEY does not exhibit such photo-reduction, all scans per run of the two sulfonamides were averaged for greater signal-to-noise ratio. Background subtraction and normalization of the spectra were achieved using BlueprintXAS. The number of components for fits were estimated by employing the Akaike information criterion (AIC). The model with the lowest AIC was chosen for fitting of all spectra; fits with smallest sum of squared errors were chosen for background subtraction and normalization which lead to the data shown in this chapter.
Chapter 4


4.1 Introduction

As the prevalence of nitric oxide (NO) and azanone (HNO) signaling in medicine and biochemistry increases, methods of generation become pivotal in drug design. Molecular carriers and releasers of NO/HNO, like azo compounds, S-nitrosothiols, and sulfonamides, can be key to directing their storage and delivery. Transmission effects through sulfur-nitrogen bonds are central to understanding the mechanism of self-decomposition in N-hydroxy sulfonamides and their subsequent release of NO/HNO.

N-hydroxy benzenesulfonamide, known also as Piloty’s acid (PA), was first synthesized by Oskar Piloty, in 1896. Work done by Angeli postulated azanone elimination via:

\[
\text{C}_6\text{H}_5\text{SO}_2\text{NHO}^{-} \rightarrow \text{C}_6\text{H}_5\text{SO}^{-} + \text{HNO}
\]  

(4.1)
Sulfonamides also act as enzyme inhibitors and antibacterials, where electronics and sterics are instrumental to their efficacy,\textsuperscript{74} \textsuperscript{3} Many studies of substituted sulfonamides seek structural connections to bacteriostatic activity. Correlation analysis using NMR, IR and UV/Vis,\textsuperscript{37,75–78} with Hammett parameters\textsuperscript{1,2,79,80} are a favored method of evaluating structural differences with bioactivity.

In this chapter, the intramolecular structure of sulfonamides and N-hydroxy sulfonamides and their potential for NO/HNO release is further studied via structure-function relationships. The sulfonamido amide nitrogen is hydroxylated and compared to the parent sulfonamide, creating an electron withdrawing effect away from the nitrogen: \(\text{CH}_3\text{O}_2\text{S} \rightarrow \text{N} \rightarrow \text{O}^\ominus \text{H}\). Modifications to the R-group are also explored; para-substitutions with a wide range of Hammett \(\sigma\) constants are used.\textsuperscript{1} These two modifications on either side of the sulfonamide S-N bond will dictate what governs the electronic structure and to that end, its ramifications on the stability of the S-N bond. As per the previous Chapter 3.2.1, sulfur K-edge XAS is used in the same manner and, in Chapter 5, is correlated to DFT calculations for further insight.

### 4.2 Results

#### 4.2.1 XAS

The S K-edge XAS spectra of the simplest system, \(\text{CH}_3\text{SO}_2\text{NH}_2\) methanesulfonamide (1a) and \(\text{CH}_3\text{SO}_2\text{NHOH}\) N-hydroxymethanesulfonamide (1b) are shown in Figure 4.2. As discussed in the previous chapter and seen in Figure 4.2, 1a has a single broad band at 2481.1 eV, as identified from the inflection point of the first derivative spectrum. Upon hydroxylation of the amide, however, a new and very interesting peak appears at 2477.2 eV, which will be referred to as peak Y. Recall, this spectrum is seen from the perspective of the sulfur atom; this new feature arising from the modification of the neighboring atom must, therefore, directly be influencing the sulfur atom. The nature of the sulfur-nitrogen bond, then, must change between the sulfonamide and the N-hydroxy sulfonamide. With the addition of a hydroxy group on the amide, the
electron withdrawing effect of oxygen could lead the nitrogen to have a partial positive charge CH₃O₂S→N⁺→O⁻H.

Figure 4.3 a) shows spectra for para-substituted aryl sulfonamides: methanesulfonamide (1a), benzenesulfonamide (2a), methoxybenzenesulfonamide (3a), toluenesulfonamide (4a), chlorobenzenesulfonamide (5a) and nitrobenzenesulfonamide (6a). In the previous chapter, the introduction of an aromatic group yielded a shoulder in the XAS spectrum, which correlated to the SC₄π bond. Here, again, all aromatic spectra display a shoulder, shifted to lower energy with respect to the main peak, in the same manner as benzenesulfonamide in the previous chapter. For the sake of simplicity, this shoulder will be referred to as peak X.

XAS spectra of all the N-hydroxy sulfonamide compounds are shown in Fig-
Figure 4.2: Sulfur K-edge XAS of methanesulfonamide (1a), black and N-hydroxy methanesulfonamide (1b), red. The appearance of a new feature at low energy indicates the significant impact of the hydroxylation of the amide to the sulfur atom.

Figure 4.3 b); the spectra mirror that of the parent compounds but with the noticeable addition. Akin to the XAS spectrum of 1b, a new feature, peak Y, emerges upon N hydroxylation. If we look at each substituent (Figures Figure 4.2 – Figure 4.8) there is an overall trend whereby the X peaks of all NOHS are shifted to lower energy than their NHS counterparts, i.e. the energy difference between the peak X of 3a and 3b is -0.6 eV. These differences range from -0.3eV to -0.85eV.

Visual inspection of the XAS spectra for N-hydroxy sulfonamides with electron donating groups (EDG), Figure Figure 4.9, reveal the lowest energy Y peaks for 3b and 2b align with the lower energy peak found in 1b, indicative that this feature does indeed pertain to nitrogen hydroxylation. Peak X for all
Figure 4.3: Sulfur K-edge X-ray absorption spectra of a) sulfonamides and b) N-hydroxysulfonamides. The lowest energy peak is labeled as Y (absent in sulfonamides), the middle energy peak is labeled as X and, the main absorption peak will be referred to as peak M.
Table 4.1: XAS energies of absorption peaks for sulfonamides (a) and N-hydroxy sulfonamides (b). Peak Y arises only with compounds b and peak X with aryl compounds. Peak M is the main absorption peak.

<table>
<thead>
<tr>
<th>Compound</th>
<th>peak Y (eV)</th>
<th>peak X (eV)</th>
<th>peak M (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td></td>
<td></td>
<td>2481.1</td>
</tr>
<tr>
<td>1b</td>
<td>2477.2</td>
<td></td>
<td>2481.3</td>
</tr>
<tr>
<td>2a</td>
<td></td>
<td>2479.3</td>
<td>2481.4</td>
</tr>
<tr>
<td>2b</td>
<td>2476.8</td>
<td>2478.8</td>
<td>2481.3</td>
</tr>
<tr>
<td>3a</td>
<td></td>
<td>2479.3</td>
<td>2481.2</td>
</tr>
<tr>
<td>3b</td>
<td>2477.1</td>
<td>2478.9</td>
<td>2481.4</td>
</tr>
<tr>
<td>4a</td>
<td></td>
<td>2479.3</td>
<td>2481.6</td>
</tr>
<tr>
<td>4b</td>
<td>2476.9</td>
<td>2478.9</td>
<td>2481.5</td>
</tr>
<tr>
<td>5a</td>
<td></td>
<td>2479.3</td>
<td>2481.4</td>
</tr>
<tr>
<td>5b</td>
<td></td>
<td>2478.8</td>
<td>2481.4</td>
</tr>
<tr>
<td>6a</td>
<td></td>
<td>2478.7</td>
<td>2481.1</td>
</tr>
<tr>
<td>6b</td>
<td>2477.2</td>
<td>2478.6</td>
<td>2481.3</td>
</tr>
</tbody>
</table>

Figure 4.4: Sulfur K-edge X-ray absorption spectra benzenesulfonamide (2a) and N-hydroxy-p-benzenesulfonamide (2b). 2a displays peak X at 2479.3 eV with the main peak at 2481.4 eV; 2b displays peak X at 2478.8 eV with the main peak 2481.3 eV, there is an appearance of a new feature, peak Y, at 2476.8 eV.
Figure 4.5: Sulfur K-edge X-ray absorption spectra p-methoxybenzene sulfonamide (3a) and N-hydroxy-p-methoxybenzene sulfonamide (3b). 3a displays peak X at 2479.3 eV with the main peak at 2481.2 eV; 3b displays peak X at 2478.9 eV with peak M at 2481.4 eV, peak Y is seen at 2477.1 eV.

Figure 4.6: Sulfur K-edge X-ray absorption spectra toluenesulfonamide (4a) and N-hydroxy-p-toluenesulfonamide (4b). 4a displays peak X at 2479.3 eV with the main peak at 2481.6 eV; 4b displays peak X at 2478.9 eV with the main peak 2481.5 eV, a lower intensity peak Y is seen at 2476.9 eV.
Figure 4.7: Sulfur K-edge X-ray absorption spectra p-chloro benzensulfonamide (5a) and N-hydroxy-p-chlorobenzene sulfonamide (5b). 5a exhibits peak X at 2479.3 eV with peak M at 2481.4 eV; 5b exhibits peak X at 2478.8 eV with the main peak 2481.4 eV, peak Y is too small to distinguish.

Figure 4.8: Sulfur K-edge X-ray absorption spectra p-nitrobenzene sulfonamide (6a) and N-hydroxy-p-nitrobenzene sulfonamide (6b). 6a exhibits peak X at 2478.7 eV with the main peak at 2481.1 eV; 6b exhibits peak X at 2478.6 eV with peak M at 2481.3 eV, peak Y is seen at 2477.2 eV.
aromatic NOHS overlap in the same region (absent in the alkyl sulfonamide) which would suggest it is related to the presence of the aromatic ring. Similarly for the electron withdrawing groups (EWG) we turn our attention to Figure 4.10. Again, peak X is present only in the aromatic sulfonamides and the lowest energy peak Y corresponds to the nitrogen hydroxylation. The difference between the electron withdrawing and electron donating groups can be seen in this ~2477eV Y peak. The intensities are lower for the EWG than the EDG. This points to an overall change in the delocalization of the electron distribution which has a direct impact in the sulfur nitrogen bond character. The XAS energies where these peaks appear do not exhibit a correlation with Hammett σ constants; so the affect of these substitutions are more complicated than a straightforward explanation of electron donation or withdrawal. Since all compounds are substituted at the para position, steric hindrance or mesomeric differences due to ortho/meta placement are not considered. A more detailed analysis, supported by DFT calculations will be discussed in the following chapter.
Figure 4.9: NOHS sulfonamides with para electron donating groups. 1b and 2b are included for reference.
Figure 4.10: NOHS sulfonamides with para electron withdrawing groups. 1b and 2b are included for reference.
4.2.2 Structure-Function Relationships

The outcome of small structural changes can be quantified and correlated with kinetic or thermodynamic reactivity via structure-function relationships, also called quantitative structure activity relationships (QSAR) or linear free energy relationships (LFER).\textsuperscript{80,81} Hammett constants were first based on the changes in the ionization equilibrium induced by structural modifications of substituted benzoic acids, equation 4.2:

\[
X-C_6H_5(C(\text{-})O)OH + H_2O \rightleftharpoons X-C_6H_5(C(\text{-})O)O\text{-} + H_3O^+ \quad (4.2)
\]

A simple formula illustrates how a substituent in the para or meta position of a phenyl ring can act upon the equilibrium of a reaction in the Hammett equation 4.3:

\[
\log\left(\frac{k_i}{k_0}\right) = \rho \sigma \quad (4.3)
\]

Where \(k_i\) is an equilibrium constant or a rate constant of the substituted reactant and \(k_0\) the commensurate quantity of the unsubstituted reactant, \(\sigma\) is the substituent constant—\(\sigma_p\) for para and \(\sigma_m\) for meta, and \(\rho\) is the reaction constant, which is dependent on the reaction, medium and temperature.\textsuperscript{1} While an empirical relationship, the use of Hammett parameters makes navigable otherwise quantitatively undefinable attributes in chemical reactions. For example, the \(^1\)H NMR chemical shift of amide protons in sulfonamides have been shown to correlate well with Hammett \(\sigma\) parameters.\textsuperscript{75,77,82}

A myriad of other constants that separate inductive and resonance effects can be found in the works of Hansch and Taft; Okamoto and Brown; and others.\textsuperscript{2,79,83} The separation of inductive and resonance \(\sigma\) constants can aid in the analysis of how a substituent influences a reactive center. For example, constants that stabilize negative charges via resonance find better linear correlation with \(\sigma^-\), based upon the ionization of para-substituted phenols. For those that stabilize positive charges via resonance, \(\sigma^+\), is based on the heterolysis of para-substituted t-cumyl chlorides.\textsuperscript{84} For this sulfonamide system, the means of substituent effects are unknown so it is best to use a range of \(\sigma\) constants to determine which will give the best correlation. In this chapter, the original
Hammett $\sigma_p$; Okamoto and Brown’s $\sigma^+$; and Hansch and Taft’s $\sigma_R^-$ (resonance to negative center), are used for QSAR tests. Values for each substituent can be found in Table 4.2. Simple linear regression analysis will determine which para-$\sigma$ constant best describes the affect of substituent effects to the sulfonamide sulfur and nitrogen atoms using NMR, IR, crystallography and XAS data. Intuitively, the $R^2$ score reflects how well a linear regression model fits its data. Given data points $x_i$ let $y_i$ be the observation at that point, $\hat{f}_i$ be the regression prediction at that point, and $\hat{y}$ be the mean response of all observations. The "goodness-of-fit" can then be written as

$$R^2 = \frac{\sum_i (f_i - \hat{y})^2}{\sum_i (y_i - \hat{y})^2}. \quad (4.4)$$

The numerator represents the amount of the signal explained by the regression model and the denominator can be roughly seen as the total variation in these observations. As a result this score can be interpreted as the total amount of variation that is explained by the regression model, where scores range between a value of 0 (a poor fit) and 1 (a perfect fit).

Table 4.2: Hammett constants used in this chapter. $\sigma_p$ from reference\textsuperscript{1} and $\sigma^+$ and $\sigma_R^-$ from reference\textsuperscript{2}

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$\sigma_p$</th>
<th>$\sigma^+$</th>
<th>$\sigma_R^-$</th>
</tr>
</thead>
<tbody>
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<td>OCH\textsubscript{3}</td>
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<td>-0.78</td>
<td>-0.27</td>
</tr>
<tr>
<td>CH\textsubscript{3}</td>
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<td>-0.31</td>
<td>0.03</td>
</tr>
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<td>H</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cl</td>
<td>0.23</td>
<td>0.11</td>
<td>-0.12</td>
</tr>
<tr>
<td>NO\textsubscript{2}</td>
<td>0.78</td>
<td>0.79</td>
<td>0.18</td>
</tr>
</tbody>
</table>
\textbf{\textsuperscript{1}H NMR}

Sulfonamide samples were prepared in a solution of $d_6$-DMSO, peaks obtained for the deuterated solvent were used as internal reference points. The sulfonamide compounds exhibit chemical shifts for the NH$_2$ protons in the 7ppm range; the amide and hydroxyl protons for the N-hydroxy sulfonamides in the 9ppm range (see Appendix A.1 for spectra). Comparison of the amide proton $\textsuperscript{1}H$ NMR chemical shift versus Hammett $\sigma_p$ results in a linear relationship, Figure Figure 4.11. The sulfonamide amide protons are shifted upfield with electron donating substituents, conversely, electron withdrawing groups are shifted downfield. This indicates that the EWG inductively causes deshielding of the amide protons. The NOHS amide proton and hydroxy proton also display a linear relationship with the Hammett $\sigma_p$ constant. We see again EDG are shifted upfield while EWG shift downfield. As per Davis et al., the slope is a measure of transmission through the sulfur-nitrogen bond. It is stipulated that the $\textsuperscript{1}H$ NMR chemical shift of the hydroxyl protons in N-arenesulfonamides hydrogen bond with the nitrogen, which in turn is a measure of electron density on nitrogen. The slope is then considered the equivalent to the reaction constant $\rho$ as proposed by the Hammett equation. If we consider hydrogen bonding of sulfonamides with DMSO we too can extend this interpretation of varying electron density on the nitrogen atom.

\begin{align*}
\text{NHS : } \delta_{\text{NH}} &= 0.50 \sigma_p + 7.34 \quad R^2 = 0.999 \quad (4.5) \\
\text{NOHS : } \delta_{\text{OH}} &= 0.44 \sigma_p + 9.60 \quad R^2 = 0.997 \quad (4.6) \\
\text{NOHS : } \delta_{\text{NH}} &= 0.44 \sigma_p + 9.55 \quad R^2 = 0.963 \quad (4.7)
\end{align*}

The proton NMR data reports excellent correlation The slopes of NHS and NOHS are very similar, equations 4.5, 4.6 and 4.7. The positive slopes of the Hammett plots indicate a sensitivity of the proton chemical shifts to EWG. As the electron-withdrawing substituents’ $\sigma_p$ become more positive, the further downfield the proton will shift. This points to an increase in the acidity of the pro-
tons and, hence, a decrease in the negativity of the nitrogen. The N-hydroxy sulfonamide protons are even more acidic, as the intercept is approximately 2 ppm higher than that of the sulfonamide. The slightly more positive sulfonamide slope indicates the substituent changes influence the NHS more than the NOHS proton.

Sigma constants that express mesomeric interactions $\sigma_R^-$ and $\sigma_P^+$ ($R^2 = 0.522$ and 0.935 respectively) do not boast as good a fit with the proton chemical shift as $\sigma_P$ ($R^2 = 0.999$) which further indicates that the substituents affect the sulfonamide moiety by induction rather than mesomeric effects; except in the case of the N-hydroxy amide proton with is best correlated to resonance with a positive center.

For the amide protons of the sulfonamides:

$$\sigma^+ : \delta_{\text{NH}} = 0.35 \sigma^+ + 7.41 \quad R^2 = 0.935 \quad (4.8)$$

$$\sigma_R^- : \delta_{\text{NH}} = 0.89 \sigma_R^- + 7.43 \quad R^2 = 0.522 \quad (4.9)$$

For the hydroxyl proton of the N-hydroxy sulfonamides:

$$\sigma^+ : \delta_{\text{OH}} = 0.30 \sigma^+ + 9.66 \quad R^2 = 0.903 \quad (4.10)$$

$$\sigma_R^- : \delta_{\text{OH}} = 0.78 \sigma_R^- + 9.68 \quad R^2 = 0.511 \quad (4.11)$$

For the amide proton of the N-hydroxy sulfonamides:

$$\sigma^+ : \delta_{\text{NH}} = 0.32 \sigma^+ + 9.61 \quad R^2 = 0.983 \quad (4.12)$$

$$\sigma_R^- : \delta_{\text{NH}} = 0.84 \sigma_R^- + 9.63 \quad R^2 = 0.570 \quad (4.13)$$
Figure 4.11: $^1$H NMR chemical shift of amide protons versus Hammett $\sigma_P$ constants, in DMSO. (a) Sulfonamide NH$_2$ proton (star). (b) N-hydroxy sulfonamide protons: OH proton (diamond), NH proton (pentagram).
**X-Ray Crystallography**

Three N-hydroxy sulfonamides were crystallized in methanol at room temperature Figure 4.12. Table 4.3 gives the bond lengths of: N-hydroxy benzenesulfonamide (2b), N-hydroxy- p-methoxy benzenesulfonamide (3b) and N-hydroxy- p-nitrobenzene sulfonamide (6b).

**Table 4.3:** Experimental bond lengths and bond angles of 2b, 3b, and 6b.

<table>
<thead>
<tr>
<th>Bond Length Å</th>
<th>3b</th>
<th>2b</th>
<th>6b</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-C</td>
<td>1.756</td>
<td>1.752</td>
<td>1.756</td>
</tr>
<tr>
<td>S-N</td>
<td>1.674</td>
<td>1.655</td>
<td>1.633</td>
</tr>
<tr>
<td>S-O</td>
<td>1.438</td>
<td>1.439</td>
<td>1.439</td>
</tr>
<tr>
<td>S-O</td>
<td>1.439</td>
<td>1.436</td>
<td>1.429</td>
</tr>
<tr>
<td>N-O</td>
<td>1.434</td>
<td>1.429</td>
<td>1.424</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Bond Angle</th>
<th>3b</th>
<th>2b</th>
<th>6b</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSN</td>
<td>108.14</td>
<td>109.14</td>
<td>106.00</td>
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<tr>
<td>OSO</td>
<td>119.37</td>
<td>119.63</td>
<td>120.67</td>
</tr>
<tr>
<td>SNO</td>
<td>109.75</td>
<td>109.50</td>
<td>110.22</td>
</tr>
<tr>
<td>CSNO</td>
<td>53.97</td>
<td>58.97</td>
<td>58.56</td>
</tr>
<tr>
<td>Hammett Parameter</td>
<td>-0.286</td>
<td>0</td>
<td>0.778</td>
</tr>
</tbody>
</table>

Figure 4.12: Crystal structures of: a) 2b, b) 3b, and c) 6b.

The sulfur-carbon bond lengths appear unaffected by the changes occur-
Figure 4.13: Hammett plots of NOHS bond lengths. a) S-N bond distances vs. $\sigma_p$, $\sigma^+$, $\sigma^-$, b) N-O bond distances vs. $\sigma_p$, $\sigma^+$, $\sigma^-$. 
ring at the para-position of the phenyl group regardless of ED or EW nature. This is interesting in light of the fact that alterations do occur in the S-N and N-O bond lengths; and these do correlate with $\sigma_p$ constants, Figure 4.13. The sulfur-nitrogen and nitrogen-oxygen bond lengths contract with electron withdrawing group. The correlation is further improved when resonance Hammett constants are used. The best fits occur when $\sigma^+$ ($R^2 = 0.999$) is employed.

For the sulfur-nitrogen bond distances:

$$\Delta S - N = -0.036 \sigma_p + 1.66 \quad R^2 = 0.953 \quad (4.14)$$

$$\Delta S - N = -0.026 \sigma^+ + 1.65 \quad R^2 = 0.998 \quad (4.15)$$

$$\Delta S - N = -0.089 \sigma^- + 1.65 \quad R^2 = 0.975 \quad (4.16)$$

For the nitrogen-oxygen bond distances:

$$\Delta N - O = -0.009 \sigma_p + 1.43 \quad R^2 = 0.933 \quad (4.17)$$

$$\Delta N - O = -0.006 \sigma^+ + 1.43 \quad R^2 = 0.999 \quad (4.18)$$

$$\Delta N - O = -0.022 \sigma^- + 1.43 \quad R^2 = 0.987 \quad (4.19)$$

The bond length of 1.755Å for the sulfur-carbon bond indicates a double bond and this bond length is consistent regardless of the nature of the para-substituent. This suggests that resonance contribution from the substituent has a small impact on the sulfonamide; instead, the contraction of the nitrogen containing bonds are due to induction. This is somewhat contrary to the QSAR which suggests resonance with a positive center. We can consider the electron poor nitrogen to be more positive, but there is no other justification for a resonance structure with the the nitrogen.

Sulfonamide S-N and S-C bond lengths from the literature are reported in
Table 4.4 for 2a (YIFZAP), 3a (IWEREI) and 6a (XUDTIZ01), from the Cambridge Crystallographic Data Center. Here, we see that the NHS S-N bonds are slightly shorter than the corresponding NOHS S-N bonds. The S-C bonds show less variation between the NOHS and NHS species. Scholz et al. reported the S-N bond length to be 0.5 Å longer in PhSO₂NHOH than PhSO₂NH₂, which is attributed to a decrease in nitrogen lone pair donation to the sulfur bonding orbitals. In the most electron-donating case (R = methoxy-benzene), the sulfur-nitrogen bond length increases by 0.062 Å upon nitrogen hydroxylation; for the most electron-withdrawing (R = nitrobenzene) the difference is +0.024 Å.

Typical N—O bond length is reported at 1.4 Å and N=O at 1.2 Å. Our values for N-O fall solidly within the bounds of a single bond. The S-N bond length of a similar functional group, S-nitrosothiols, report S—N 1.6–1.8 Å and S—N ~1.5 Å. These values suggest a single bond between the sulfur-nitrogen, for both NHS and NOHS.

**Table 4.4:** Experimental bond lengths of 2a (YIFZAP), 3a (IWEREI), and 6a (XUDTIZ01).

<table>
<thead>
<tr>
<th>Bond Length Å</th>
<th>3a</th>
<th>2a</th>
<th>6a</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-C</td>
<td>1.761</td>
<td>1.754</td>
<td>1.770</td>
</tr>
<tr>
<td>S-N</td>
<td>1.612</td>
<td>1.598</td>
<td>1.609</td>
</tr>
<tr>
<td>Hammett Parameter</td>
<td>-0.286</td>
<td>0</td>
<td>0.778</td>
</tr>
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</table>

**IR**

Infrared spectroscopy has also been used to evaluate affects of substituents on the sulfonamide group. Solid state samples of all NHS and NOHS were measured using attenuated total reflectance-FTIR, spectra are in Appendix A.2. Characteristic frequencies for sulfonamides are the ν(NH₂) at 3100–3490 cm⁻¹, νa(SO₂) at 1330–1380 cm⁻¹, νs(SO₂) at 1140–1170 cm⁻¹ and ν(SN) at 860–950 cm⁻¹.

Table Table 4.5 reports the stretching frequencies for all NHS and NOHS. Vibrational frequencies of the bonds associated with the sulfur and nitrogen
atoms blueshift upon amide hydroxylation, indicating an increase in the strength of bonds associated with the sulfur and nitrogen atoms. The changes are not systematic with the substituent effects. The only frequency to show agreement with $\sigma_p$ are the NOHS $\nu$(SN). Within the NOHS compounds the S-N stretch redshifts as the substituent becomes more electron withdrawing; which points to a weakening of the sulfur-nitrogen bond. The vibrational data point to the amide substitution being the greater contributor to the overall molecular structure than the substituents at the para-phenyl position.

**Table 4.5**: Stretching frequencies for sulfonamides and N-hydroxy sulfonamides.

<table>
<thead>
<tr>
<th>Wavenumber (cm$^{-1}$)</th>
<th>$\nu_a$ (NH$_2$)</th>
<th>$\nu_s$ (NH$_2$)</th>
<th>$\nu_a$ (SO$_2$)</th>
<th>$\nu_s$ (SO$_2$)</th>
<th>$\nu$ (SN)</th>
<th>$\nu$ (CS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>3321</td>
<td>3257</td>
<td>1307</td>
<td>1144</td>
<td>876</td>
<td>766</td>
</tr>
<tr>
<td>1b</td>
<td>3375</td>
<td>3254</td>
<td>1320</td>
<td>1158</td>
<td>900</td>
<td>788</td>
</tr>
<tr>
<td>2a</td>
<td>3345</td>
<td>3250</td>
<td>1310</td>
<td>1153</td>
<td>902</td>
<td>754</td>
</tr>
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<td>2b</td>
<td>3438</td>
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<td>1321</td>
<td>1161</td>
<td>922</td>
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</tr>
<tr>
<td>3a</td>
<td>3343</td>
<td>3266</td>
<td>1300</td>
<td>1103</td>
<td>912</td>
<td>800</td>
</tr>
<tr>
<td>3b</td>
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<td>1325</td>
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<td>944</td>
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<td>1162</td>
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<td>6b</td>
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<td>3247</td>
<td>1343</td>
<td>1161</td>
<td>914</td>
<td>742</td>
</tr>
</tbody>
</table>

\[
\nu \text{ (SN)} = -27.66 \sigma_p + 930.64 \quad R^2 = 0.740 \quad (4.20)
\]

\[
\nu \text{ (SN)} = -23.33 \sigma^+ + 926.79 \quad R^2 = 0.829 \quad (4.21)
\]

\[
\nu \text{ (SN)} = -46.90 \sigma^- + 925.91 \quad R^2 = 0.343 \quad (4.22)
\]

The slopes for $\rho$ show poor fit, which is unsurprising as the vibrational frequencies are not systematic with Hammett constants. The best fit, however, is
Figure 4.14: Hammett plot of $\nu$ (SN) vs. $\sigma_p, \sigma^+, \sigma_R$

still given by $\sigma^+$ with resonance interaction with the sulfonamide moiety.
XAS

The energies at which the Y and X peaks appear in the XAS data do not correlate well with $\sigma_p$. We do, however, see an interesting trend with the intensities of the low energy feature, see Figure 4.3 b) at ~2477 eV: 2b at 1.15, 3b at 1.87, 4b at 0.36, 6b at 0.90, and at 5b no peak is seen. These peaks show signs of correlation to those substituents which have inherent resonance. The methyl and chloro substituents will not partake in as strong a mesomeric effect with the phenyl ring as the nitro and methoxy groups will. A comparison of $\sigma_p$ with resonance inclusion parameters are seen in Figure 4.15.

Intensity at 2477 eV = $-0.501 \sigma_p + 0.913 \quad R^2 = 0.083$  \hspace{1cm} (4.23)

Intensity at 2477 eV = $-0.522 \sigma^* + 0.836 \quad R^2 = 0.174$  \hspace{1cm} (4.24)

Intensity at 2477 eV = $-1.560 \sigma^- + 0.799 \quad R^2 = 0.133$  \hspace{1cm} (4.25)

The poor correlation of the XAS intensities to the inductive parameter is clear ($R^2 = 0.083$); the resonance parameters are little help to the relationship. This is not too surprising as XAS conveys a different perspective. XAS spectra reveal the anti-bonding MOs, whereupon the bonding MOs can be deduced. Induction is not a property that can be seen easily within the MO framework. Resonance factors, though they show poor correlation here, however, can be seen within the MO framework and will be further explored in the following chapter with DFT calculations. The minimal differences seen between the substituents’ XAS spectra suggest that the substituent effect has a smaller impact to the bonding framework than the amide hydroxylation.
4.3 Discussion

The structure-function relationships shown using NMR, IR, X-ray crystallography and XAS point to a system where induction and resonance effects work in a complicated manner. The NMR chemical shift and crystallography bond lengths correlate well with Hammett parameters and indicate that the substituents do affect the framework of the molecular bonding. The structure parameters which include resonance with the sulfonamide center increase corollary relationships; however, a lack of correlation with substituent in the vibrational and absorption spectra suggests the hydroxylation of the amide as far more important than the substituent effect. The greater changes in the crystallography, IR and XAS are always connected to the amide substitution, not the R-group modifications.

It has been noted that the reactivity of the primary amino group is most im-

Figure 4.15: Hammett plot of intensities of low energy feature, at approxi-
mately 2477eV, found in N-hydroxysulfonamide XAS spectra vs. $\sigma_p$, $\sigma^+$, $\sigma^-$. 
important for sulfonamide activity,\textsuperscript{76} which supports the QSAR data shown in this thesis. NMR studies of anilines and carboxamides agree with the NMR data shown here\textsuperscript{82,88} and can be used to draw parallels. The comparison of aniline NMR QSAR shows a similar plot, of differing $\rho$ value,\textsuperscript{88} where the aniline protons are shifted most downfield with electron-withdrawing groups, implying a decrease in the nitrogen negativity; the addition of a hydroxyl group on the amide further pulls electron density away from the nitrogen, perturbing the bond between the sulfur and nitrogen. This is consistent with the contraction of bond length seen in the crystallography. For the sulfonamides, the crystallography and XAS data imply a sulfur-carbon double bond for both EWG and EDG, however, Lewis diagrams do not support this, Scheme Scheme 4.1.

The general good fit for $\sigma^+$ within the QSAR tests indicate EDGs at the para position will stabilize the electron poor nitrogen, and EWG will destabilize this bond leading to potential cleavage of S-N; this affect may not be strictly due to resonance affects as implied by $\sigma^+$, or Scheme Scheme 4.1. Anecdotally, the only compound for which IR was not acquired was for 6a (nitrobenzenesulfonamide) as it had already decomposed to a sulfoxide. This affect may be more pronounced in the sulfonamides, as they are without the stabilizing EWG of the hydroxyl oxygen. What is made clear from the QSAR is that the substituent effect is small and non-systematic and that the amide hydroxylation is much more important to the bonding framework, as seen in Scheme Scheme 4.2.

According to calculations in the previous chapter and the low energy feature found in XAS spectra this points to further evidence that there is some bond multiplicity occurring within the sulfonamide S-N. DFT calculations in the following chapter will elaborate on this statement.

\section*{4.4 Experimental}

\subsection*{4.4.1 General Considerations}

Sulfonamides used in this study were purchased from Sigma-Aldrich (98-99% purity). $^1$H NMR spectra were collected on a Bruker Avance 300 MHz or 400MHz spectrometer at ambient temperature. $^1$H NMR chemical shifts are
Scheme 4.1: Lewis diagrams of sulfonamides with EWG and EDG groups. Aniline is shown as a comparison.

Scheme 4.2: Inductions effects of N-hydroxy sulfonamide with EWG and EDG.
reported in ppm versus residual protons in deuterated solvents as follows: \( \delta \) 2.50, DMSO-d6 and 3.33, water. ATR-FTIR were performed on solid samples using PerkinElmer Frontier FT-IR spectrometer. Mass spectrometry was performed using electron impact ionization mass spectrometer Kratos MS-50. CHN Elemental analysis were performed using a Carlo Erba EA1108 elemental analyzer. Diffraction measurements for X-ray crystallography were made on a Bruker X8 APEX II diffraction with graphite monochromated Mo-K\( \alpha \) radiation. The structures were solved by direct methods and refined by full-matrix least-squares using the SHELXTL crystallographic software of Bruker-AXS. Unless specified, all non-hydrogens were refined with anisotropic displacement parameters, and all hydrogen atoms were constrained to geometrically calculated positions but were not refined.

**Synthesis of N-hydroxy-benzenesulfonamide (2b).** N-hydroxy benzenesulfonamide was prepared as reported in literature.\(^8\)\(^9\)\(^0\) Hydroxylamine hydrochloride (1.44g, 20mmol) in 10mL MeOH-H\( _2 \)O (3:2) was treated with MgO (0.68g, 8.6mmol). A solution of sulfonyl chloride (8.6mmol) in THF (60mL) was then added and mixed vigorously. A second batch of MgO (0.34g, 4.3mmol) was added and the reaction was vigorously stirred for 12-18h at RT. TLC (EtOAc-hexane, 2:1) was used to confirm the disappearance of the sulfonyl chloride starting material, the mixture was then filtered through Whatman paper, concentrated and purified using Silicycle TLC prep plates with EtOAc-hexane, 2:1, eluent. High conversion, low purification. The band corresponding to the N-hydroxysulfonamide was extracted from silica with 80-20% MeOH:DCM, filtered and evaporated to dryness. A white solid was collected. Crude material was recrystallized in methanol at RT to yield white crystals. \(^1\)H NMR (300 MHz, DMSO) \( \delta \) 9.59 (m, 2H), 7.84 (d, 2H, \( J=9 \)Hz), 7.63 (m, 3H, \( J=13 \)Hz). IR (ATR-FTIR) \( \nu \)(OH) 3438 cm\(^{-1}\), \( \nu \)(NH) 3245 cm\(^{-1}\), \( \nu \)(SO)\(^a\) 1321 cm\(^{-1}\), \( \nu \)(SO)\(^s\) 1161 cm\(^{-1}\), \( \nu \)(SN) 922 cm\(^{-1}\). LRMS (EI): m/z Calculated: 173, Obtained: 173. Elemental Analysis calculated for (C\(_6\)H\(_7\)NO\(_3\)S + 0.3C\(_4\)H\(_8\)O\(_2\) + 0.1CH\(_2\)Cl\(_2\)): C, 42.13; H, 4.65; N, 6.73. Obtained: C, 41.95; H, 4.32; N, 6.44.

**Synthesis of N-hydroxy-p-methoxybenzenesulfonamide (3b).** N-hydroxy p-methoxybenzenesulfonamide was prepared as described for (2b). A white
solid was collected. The crude material was recrystallized in methanol at RT to yield white crystals. \(^1\)H NMR (300 MHz, DMSO) \(\delta \) 9.53 (s, 1H), 9.48 (s, 1H), 7.72 (d, 2H, \(J=9\)Hz), 7.42 (d, 2H, \(J=9\)Hz), 2.40 (s, 3H). IR (ATR-FTIR) \(\nu(\text{OH}) \) 3375 cm\(^{-1}\), \(\nu(\text{NH}) \) 3354 cm\(^{-1}\), \(\nu(\text{SO})_a \) 1346 cm\(^{-1}\), \(\nu(\text{SO})_s \) 1161 cm\(^{-1}\), \(\nu(\text{SN}) \) 940 cm\(^{-1}\). LRMS (ESI): m/z \([\text{M+Na}^+]\) 226.2; (EI) Calculated: 203, Obtained: 203. Elemental Analysis calculated for \((\text{C}_7\text{H}_9\text{NO}_4\text{S} \cdot 1.45\text{C}_4\text{H}_8\text{O}_2 \cdot 0.8\text{CH}_2\text{Cl}_2)\): C, 40.95; H, 5.61; N, 3.51. Obtained: C, 41.47; H, 4.98; N, 2.87. EA does not hit, due to apparent hydrolysis during analysis.

**Synthesis of N-hydroxy-toluencesulfonamide (4b).** N-hydroxy toluene-sulfonamide was prepared as described for (2b). A white solid was collected. \(^1\)H NMR (300 MHz, DMSO) \(\delta \) 9.49 (s, 1H), 9.38 (s, 1H), 7.76 (d, 2H, \(J=9\)Hz), 7.14 (d, 2H, \(J=9\)Hz), 3.85 (s, 3H). IR (ATR-FTIR) \(\nu(\text{OH}) \) 3375 cm\(^{-1}\), \(\nu(\text{NH}) \) 3354 cm\(^{-1}\), \(\nu(\text{SO})_a \) 1346 cm\(^{-1}\), \(\nu(\text{SO})_s \) 1161 cm\(^{-1}\), \(\nu(\text{SN}) \) 940 cm\(^{-1}\). LRMS (ESI): m/z \([\text{M+Na}^+]\) 209.9; (EI) Calculated: 187, Obtained: 187. Elemental Analysis calculated for \((\text{C}_7\text{H}_9\text{NO}_3\text{S})\): C, 44.91; H, 4.85; N, 7.48. Obtained: C, 44.90; H, 4.87; N, 7.24.

**Synthesis of N-hydroxy-p-chlorobenzenesulfonamide (5b).** N-hydroxy p-chlorobenzenesulfonamide was prepared as described for (2b). A white solid was collected. \(^1\)H NMR (300 MHz, DMSO) \(\delta \) 9.69 (s, 1H), 9.67 (s, 1H), 7.84 (d, 2H, \(J=9\)Hz), 7.72 (d, 2H, \(J=9\)Hz). LRMS (EI): m/z Calculated: 207, Obtained: 207. Elemental Analysis calculated for \((\text{C}_6\text{H}_6\text{NO}_3\text{SCl} \cdot 0.15\text{C}_4\text{H}_8\text{O}_2 \cdot 0.15\text{CH}_2\text{Cl}_2)\): C, 34.71; H, 3.24; N, 6. Obtained: C, 34.81; H, 3.06; N, 5.87.

**Synthesis of N-hydroxy-p-nitrobenzenesulfonamide (6b).** N-hydroxy p-nitrobenzenesulfonamide was prepared as described for (2b). A yellowish-white solid was collected. The crude material was recrystallized in methanol at RT to yield white crystals. \(^1\)H NMR (300 MHz, DMSO) \(\delta \) 9.95 (s, 1H), 9.87 (s, 1H), 8.46 (d, 2H, \(J=9\)Hz), 8.09 (d, 2H, \(J=9\)Hz). IR (ATR-FTIR) \(\nu(\text{OH}) \) 3448 cm\(^{-1}\), \(\nu(\text{NH}) \) 3247 cm\(^{-1}\), \(\nu(\text{SO})_a \) 1343 cm\(^{-1}\), \(\nu(\text{SO})_s \) 1161 cm\(^{-1}\), \(\nu(\text{SN}) \) 914 cm\(^{-1}\). LRMS (EI): m/z Calculated: 218, Obtained: 218. Elemental Analysis for \((\text{C}_6\text{H}_6\text{N}_2\text{O}_2\text{S} \cdot 0.25\text{C}_4\text{H}_8\text{O}_2 \cdot 0.1\text{CH}_2\text{Cl}_2)\): C, 34.29; H, 3.22; N, 11.26. Ob-

**Synthesis of N-hydroxy-methylsulfonamide (1b).** N-hydroxy methylsulfonamide was prepared as described for (2b). A white solid was collected. \( ^1H \) NMR (300 MHz, DMSO) \( \delta \) 9.56 (s, 1H), 9.03 (s, 1H), 2.92 (s, 3H). LRMS (ESI): m/z [M+Na\(^+\)] 134. Elemental Analysis calculated for (CH\(_5\)NO\(_3\)S*0.05C\(_4\)H\(_8\)O\(_2\) * 0.05CH\(_2\)Cl\(_2\)): C, 12.54; H, 4.63; N, 11.69. Obtained: C, 12.37; H, 4.53; N, 11.59.

### 4.4.2 XAS Acquisition and Data Analysis

Sulfur K-edge XAS data for potassium dinitrososulfite and tertbutanesulfinamide were acquired at Stanford Synchrotron Radiation Lightsource (SSRL). Fluorescence data were collected at beamline 4-3 at the Stanford Synchrotron Radiation Lightsource (SSRL) under ring conditions of 3GeV and 60-100mA. Solid samples were ground finely with 50% boron nitride, to minimize self-absorption, and mounted as a thin layer on sulfur-free Kapton tape at room temperature. Fluorescence data were acquired using solid state detector at ambient temperature and pressure. Energy calibration was carried out using sodium thiosulfate (Na\(_2\)S\(_2\)O\(_3\)) with the first pre-edge feature being calibrated at 2472.02 eV.

Sulfur K-edge XAS data for methanesulfonamide and benzenesulfonamide were acquired at the Canadian Light Source. Total electron yield data were acquired at beamline SXRMB at the CLS under ring conditions of 3 GeV and 180-250mA. Solid samples were ground finely with 50% boron nitride and mounted onto a copper sample holder with carbon tape. Total electron yield data were acquired under vacuum at ambient temperature. Calibrations were performed as above.

Raw data were normalized to incoming beam (Io), calibrated and averaged with the BlueprintXAS 60 prefit function. Due to sulfur self-absorption in fluorescence data, only the first scans of each run were used for tertbutanesulfinamide and potassium dinitrososulfite. As TEY does not exhibit such self-absorption, all scans per run of the two sulfonamides were averaged for greater signal-
to-noise ratio. Background subtraction and normalization of the spectra were achieved using BlueprintXAS.\textsuperscript{61} The number of components for fits were estimated by employing the Akaike information criterion (AIC).\textsuperscript{62,63} The model with the lowest AIC was chosen for fitting of all spectra; fits with smallest sum of squared errors were chosen for background subtraction and normalization which lead to the data shown in this thesis.
Chapter 5

Computational Analysis of Para-Substituent and Amide Hydroxylation in Sulfonamides

5.1 Introduction

It has been previously shown that simulated DFT sulfur K-edge XAS spectra for sulfur containing molecules like sulfonates and thiols agree well with experimental XAS data.\(^{91–93}\) In the work of Martin-Diaconescu et al., the XAS spectrum of p-toluene sulfonic acid exhibits a main absorption peak at 2481.7eV and a shoulder at 2479.9eV. TD-DFT calculations assigned the shoulder transition to be a SOH\(_\sigma^+\) with a \(\phi\)\(_5\pi^+\) contribution and the main peak to be a SO/SC\(_\sigma^+\) transition.\(^{39}\)

Good agreement between DFT calculations and experimental spectra have been established for S-nitrosothiols (RSNO), similar to sulfonamides. Szilagyi et al. show that for S-nitroso-N-acetylpenicillamine and S-nitroso-glutathione, the shoulder at \(\sim2471\) is due to the ON-S\(_\pi^+\) interaction, the main peak at 2473eV to the ON-S\(_\sigma^+\) transition.\(^{42}\)

As sulfonamides and N-hydroxysulfonamides bear similarities to these compounds, a reasonable description of the electronic distribution of sulfonamides...
and the affects of substituent changes and amide hydroxylation should be attained. DFT calculations of all the compounds used in Chapter 4 are used to reconstruct the XAS data and to interpret the spectra.

5.1.1 DFT Calculations

As described in Chapter 3.2.2 of this thesis, XAS simulations are calculated using TD-DFT excitation at the BP86/TZVP level of theory using ORCA, version 2.9.0. Simulated spectra for 1a and 2a, are shown in Figures 3.2 and 3.7, respectively. The simulated spectra present satisfactory agreement to the experimental data. Using the same parameters, N-hydroxy methanesulfonamide (1b) and N-hydroxy benzenesulfonamide (2b) undergo similar treatment.

Figure 5.1 shows the simulated sulfur K-edge XAS spectrum of 1b. Intriguingly, the prominent low energy feature is not reproduced in the calculated spectrum. The calculated Kohn-Sham LUMO for 1b indicates a $\text{SN}_\pi^*$ molecular orbital with 10.1% $\text{S}_3p$ and 15.3% $\text{N}_2p$ character, this is different from 1a LUMO in that the sulfur no longer shares electron density with the methyl carbon, instead directing its electron density directly along the sulfur-nitrogen bond. The LUMO+1 to be a $\text{SN}_\sigma^*$ with 14.5% $\text{S}_3p$ and 13.2% $\text{N}_2p$ character. LUMO+2 is $\text{SC}_\sigma^*$ with 18.4% $\text{C}_2p$ and 6.3% $\text{S}_3p$, LUMO+3 has 16.8% $\text{O}_2p$ and 24.9% $\text{S}_3p$ shared in a $\text{SO}_\pi^*$ with some $\text{SC}_\sigma^*$ character. This breakdown of 1b is not so different to the assessment of 1a, with the exception of the sulfur-nitrogen transitions moving to lower MOs; which suggests that the hydroxylation of the amide has small impact on the DFT calculation of the electronic contribution.

Using 2b as a model for the aryl NOHS, see Figure 5.2; the LUMO is a $\text{SC}_\pi^*$ with 20.6% $\text{C}_2p$ and 5.6% $\text{S}_3p$ contribution to the MO. LUMO+1 has no sulfur interactions but a $\phi_4$ contribution from the phenyl ring. LUMO+2 displays $\text{SCNO}_\sigma^*$ where the electron density of the sulfur atom is shared amongst its neighbors almost equally. The LUMO+3 $\text{SN}_\pi^*$ and $\text{NO}_\sigma^*$ character. Once again, this is similar to the result of 2a. The DFT calculations fall short of predicting the changes that occur upon hydroxylation and downplays the importance of the
added amide hydroxyl. Herein, lies a very interesting point, until now DFT calculations using the BP86/TZVP level of theory have satisfactorily described experimental XAS data \cite{4,39,54} and yet, now fails to include the impact of the -OH on the sulfonamide as is seen in the experimental data. Is this occurring because there are shortcomings in the calculations? Or are we misattributing the appearance of this new peak to the wrong moiety?

In order to rule out a flaw through the usage of a too small basis set or an incompatible functional, a thorough test was conducted. Geometry optimizations were performed on N-hydroxybenzenesulfonamide (2b) with eight of the most commonly used functionals: BP86,\cite{94,95} B3LYP,\cite{96,97} PW91,\cite{98} mPW-WPW,\cite{99} mPW1PW,\cite{99} BHLYP,\cite{100} B2PLYP-D\cite{101} and mPW2PLYP-D.\cite{99,101} An array of def2 Ahlrichs group basis sets were also used with each functional: def2-SVP, def2-TZVP, def2-TZVPP, def2-aug-TZVPP and def2-QZVPP.\cite{102} Each set of functional/basis set combinations were run once with and once without relativistic effects using ZORA. Bond distances from the optimized geometries for each functional/basis set were then compared to the crystal structure of 2b, see Figure Figure 4.12. The functional/basis set combination that reproduced the bond lengths most accurately and within a reasonable computational time frame were selected for use.

The def2-TZVP basis set returned the most reasonable geometry optimizations per each functional without adding extended computational time. The bond length differences of all sulfur containing bond distances from each functional are shown in Figure Figure 5.3. The geometry optimizations from mPW1PW/def2-TZVP, B3LYP/def2-TZVP, BHLYP/def2-TZVP and mPW2PLYPD/def2-TZVP levels of theory produced the smallest differences in the sulfur bond distances with mPW1PW and BHLYP underestimating, and B3LYP and mPW2 PLYPD overestimating the bond lengths. While approximating the bond distances best, mPW2PLYPD was not used in further calculations as the computational time for this geometry optimization ran for approximately 28 days; in contrast the geometry optimization using BHLYP took approximately 10 hours. The sulfur-carbon, sulfur-nitrogen, sulfur-oxygen and nitrogen-oxygen bonds, Figure Figure 5.4, were best reproduced with BHLYP followed by mPW1PW. As a result, BHLYP and mPW1PW were used for further DFT analysis. The
(a) Comparison of experimental and DFT simulated spectra of 1b.

(b) Calculated energy levels and electron density diagrams for the first six molecular orbitals.

Figure 5.1: BP86/TZVP simulation of experimental S K-edge XAS spectrum of N-hydroxy methanesulfonamide
(a) Comparison of experimental and DFT simulated spectra of 2b.

(b) Calculated energy levels and electron density diagrams for the first six molecular orbitals of 2b.

**Figure 5.2:** BP86/TZVP simulation of experimental S K-edge XAS spectrum of N-hydroxy benzenesulfonamide.
Figure 5.3: Difference of averaged bond lengths by functional. The SN, SC and both SO bond distances for each functional were averaged and subtracted from the bond lengths found using crystallography. Bond distances using mPW1PW and BHLYP underestimated the experimental bond lengths while the other functionals overestimated.

Figure 5.4: Difference of bond length, in angstrom, between the functional and the crystallographic data, for each bond length associated with the sulfur and nitrogen atoms in the sulfonamide moiety.
inclusion of relativistic effects did not improve the geometries while extending the computational time, as such, ZORA was not used in further calculations. For a complete table of bond lengths via functional and basis set, please see Appendix B.1.

**Table 5.1:** Experimental bond distances and angles of 2b, N-hydroxy benzenesulfonamide, from crystal structure, and calculated using BHLYP/def2-TZVP, mPW1PW/def2-TZVP and BP86/TZVP.

<table>
<thead>
<tr>
<th>Bond Length (Å)</th>
<th>XTAL</th>
<th>BHLYP</th>
<th>mPW1PW</th>
<th>BP86</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-C</td>
<td>1.752</td>
<td>1.756</td>
<td>1.763</td>
<td>1.786</td>
</tr>
<tr>
<td>S-N</td>
<td>1.655</td>
<td>1.661</td>
<td>1.678</td>
<td>1.724</td>
</tr>
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<td>S-O</td>
<td>1.439</td>
<td>1.417</td>
<td>1.429</td>
<td>1.451</td>
</tr>
<tr>
<td>S-O</td>
<td>1.436</td>
<td>1.415</td>
<td>1.427</td>
<td>1.449</td>
</tr>
<tr>
<td>N-O</td>
<td>1.429</td>
<td>1.390</td>
<td>1.399</td>
<td>1.433</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond Angle (°)</th>
<th>XTAL</th>
<th>BHLYP</th>
<th>mPW1PW</th>
<th>BP86</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSN</td>
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<td>106.95</td>
<td>107.11</td>
<td>103.02</td>
</tr>
<tr>
<td>OSO</td>
<td>119.63</td>
<td>122.48</td>
<td>122.78</td>
<td>122.45</td>
</tr>
<tr>
<td>SNO</td>
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<td>112.78</td>
<td>112.71</td>
<td>110.72</td>
</tr>
<tr>
<td>CSNO</td>
<td>58.97</td>
<td>56.73</td>
<td>57.17</td>
<td>86.22</td>
</tr>
</tbody>
</table>

The BHLYP and mPW1PW functionals (both with def2-TZVP basis, henceforth, this will be assumed for all BHLYP and mPW1PW calculations that follow) best approximated the crystal structure of 2b and, hence, were chosen to carry out XAS spectroscopic simulation. Reassessment of 1a (methanesulfonamide), 1b (N-hydroxy methanesulfonamide), 2a (benzenesulfonamide) and 2b (N-hydroxy benzenesulfonamide) were carried out with both functionals. Excited state calculations and XAS simulations were conducted with TDDFT and XES. The energies calculated for XAS were shifted by +49.5 eV and +20.5 eV for mPW1PW and BHLYP, respectively, to match with the experimental spectra and are shown in Figures Figure 5.5 – Figure 5.12. Since the main reason for these calculations is the reproduction of the peak at 2477eV, only the first five MOs and their contributions to the shape of the simulated spectrum will be discussed.
The spectra for 1a, Figures Figure 5.5 and Figure 5.6, with both functionals look similar to the BP86/TZVP level calculated spectra and show fair agreement with the experimental data, see Appendix B.2 for comparative spectra. Upon examination of the BHLYP MO representations, we see the LUMO and LUMO+1 have a small contribution to the shape of the spectrum. The greater contributors LUMO+2 and LUMO+3 are the \( \text{SN}_{\pi^*} \) and \( \text{SN}_{\sigma^*} \), and LUMO+4 and LUMO+5 represent \( \text{SC}_{\pi^*} \) and \( \text{SC}_{\sigma^*} \) transitions, respectively. Similar results are attained for the MO descriptions with the mPW1PW functional but with smaller energy differences between the sulfur-nitrogen and sulfur-carbon transitions. These predictions resemble those made by the BP86 functional, so in the case of methanesulfonamide the use of different functionals do not lead to disparities in the description of the electronic structure.

Upon hydroxylation of the methanesulfonamide nitrogen, the XAS clearly exhibits a new feature, which must directly relate to this modification. Will the change in functionals help describe this peak? Figures Figure 5.5 and Figure 5.6 show the results of the amended calculations; the peak at ~2477 is not reproduced with either of the functionals but an assessment of the MOs could still describe the what is seen in the experimental spectrum. Interestingly, the similarities that arose in the functionals for the 1a calculations now begin to diverge. The BHLYP excited state MO calculations show that the LUMO has almost no contribution to the simulated XAS shape; LUMO+4, LUMO+6 and LUMO+7 are the greater contributors. LUMO+1 has transitions to a \( \text{SO}_{\sigma^*} \) and \( \text{NO}_{\sigma^*} \), LUMO+4 is a \( \text{SC}_{\sigma^*} \) transition, LUMO+6 is the \( \text{SN}_{\sigma^*} \), and LUMO+7 a \( \text{SO}_{\pi^*} \) with a bit of \( \text{SN}_{\pi^*} \). For mPW1PW the LUMO is now a \( \text{SN}_{\pi^*} \), and LUMO+1 is \( \text{SO}_{\sigma^*} \) and \( \text{NO}_{\sigma^*} \), again these first two MOs do not contribute greatly to the overall shape, but if they were to be shifted to lower energy, could be seen as reproducing the lower edge feature. LUMOs 2–5 make up the main peak and are: LUMO+2 \( \text{SO}_{\pi^*} \) and a small \( \text{SC}_{\sigma^*} \), LUMO+4 an \( \text{SC}_{\sigma^*} \) along the sulfur-carbon bond axis and LUMO+4 is predominately \( \text{SN}_{\sigma^*} \) with some sulfur-oxygen mixing.

For the alkysulfonamides the effect of the different functionals on the N-hydroxy produced mixed results. How much of a difference will there be in the case of the the arylsulfonamides? In the BP86 calculations for both 2a
(a) Comparison of experimental and DFT simulated spectra of 1a.

(b) Calculated energy levels and electron density diagrams for the first six molecular orbitals of 1a.

**Figure 5.5:** BHLYP/def2-TZVP simulation of experimental S K-edge XAS spectrum of methanesulfonamide.
(a) Comparison of experimental and DFT simulated spectra of 1a.

(b) Calculated energy levels and electron density diagrams for the first six molecular orbitals of 1a.

**Figure 5.6**: mPW1PW/def2-TZVP simulation of experimental S K-edge XAS spectrum of methanesulfonamide.
(a) Comparison of experimental and DFT simulated spectra of 1a.

(b) Calculated energy levels and electron density diagrams for the first six molecular orbitals of 1b.

Figure 5.7: BHLYP/def2-TZVP simulation of experimental S K-edge XAS spectrum of N-hydroxy methanesulfonamide.
(a) Comparison of experimental and DFT simulated spectra of 1b.

(b) Calculated energy levels and electron density diagrams for the first six molecular orbitals of 1b.

**Figure 5.8:** mPW1PW/def2-TZVP simulation of experimental S K-edge XAS spectrum of N-hydroxy methanesulfonamide.
and 2b, the LUMO was a sulfur-carbon π*-mixed with electron density about the phenyl ring, the LUMO+1 had no sulfur contribution, all of the electron density being centralized on the ring, as seen in Figure 5.2. The first three MOs of benzenesulfonamide using BP86, BHLYP, and mPW1PW are the same, though their respective contributions to the spectrum vary. The similarities go further for both BHLYP and mPW1PW as the first five MOs are the same. For BHLYP LUMO (SCπ*), LUMO+6 (SOπ*), LUMO+9 (SN) and LUMO+11 (SN and SO mixing) make up the shoulder and main peak of 2a. For mPW1PW: LUMO (SCπ*), LUMO+5 (SNπ*) and LUMO+8 (SN and SO mixing) are the important MOs. Again, for a sulfonamide the differences in functional do not cause great deviations in description of the XAS spectrum.

The addition of the hydroxyl group to benzenesulfonamide results in an additional shoulder to the sulfur K-edge XAS, will BHLYP or mPW1PW accurately reproduce these features? Once more, the first two MOs of all three functionals are the same: LUMO is a sulfur-carbon π*- and LUMO+1 a ψ5 configuration. As it was in the case of 2a, the first four MOs are the same for both BHLYP and mPW1PW, and in neither is the new shoulder replicated. The major contributors for BHLYP, Figure 5.9, are LUMO, LUMO+6 (SNOπ*) and LUMO+10 (SNO mixing). Major contributors for mPW1PW, Figure 5.10 are LUMO, LUMO+4 (NOπ*, with the amide oxygen), LUMO+9 (SCNπ*) and LUMO+11 (CSONπ*). It is clear that one of these lower energy features represent the sulfur-carbon π* interaction introduced with the aryl substituent. The XAS data suggest the shoulder to be this sulfur-carbon π*, Figure 4.3a. What the other feature is, however, is still debatable. As seen in Figure Figure 4.3b the peak at 2477eV is consistent through all of the N-hydroxysulfonamides, alkyl and aryl. This feature should pertain not to the SCπ* but to some sulfur-nitrogen interaction. Perhaps, then, we could surmise that the first “high intensity” MO —after LUMO— represents the electron density configuration for this feature but at the wrong energy. For BP86 and BHLYP these would be LUMO+3 and LUMO+6, respectively, which happen to be very similar: a sulfur-nitrogen π* and nitrogen-amide oxygen σ*. For mPW1PW it is a mixing of sulfur-nitrogen-amide oxygen σ* in LUMO+4, Figure 5.13. That these MOs would represent sulfur-nitrogen interactions is logical as the added hydroxyl group should
(a) Comparison of experimental and DFT simulated spectra of 1a.

(b) Calculated energy levels and electron density diagrams for the first six molecular orbitals of 2a.

**Figure 5.9:** BHLYP/def2-TZVP simulation of experimental S K-edge XAS spectrum of benzenesulfonamide.
Figure 5.10: mPW1PW/def2-TZVP simulation of experimental S K-edge XAS spectrum of benzenesulfonamide.
directly affect these atoms.

The calculations with both functionals for the remaining compounds (by substituent: p- methoxybenzene (3), p- toluene (4), p- chlorobenzene (5), p- nitrobenzene (6)) are shown in Figures Figure 5.14— Figure 5.21. For all compounds, both sulfonamide and N-hydroxysulfonamide, EWG or EDG substituent, regardless of functional, the first two MOs are the same as for 2a and 2b. LUMO is a sulfur-carbon_\pi^* with the phenyl ring in a _\phi_4 configuration and LUMO+1 a _\phi_5 configuration. This time, however, substituent effects begin to change the shape of the simulated spectra, and some agree reasonably well. Further inspection into the calculations for N-hydroxy-p- toluenesulfonamide (4b) and N-hydroxy-p- chlorobenzenesulfonamide (5b), mPW1PW in particular, follows.

An assessment of 4b-BHLYP, Figure Figure 5.17a), shows LUMO and LUMO+7 to be the largest contributors to the shape of the lower energy peak and shoulder. The LUMO+7 for 4b is the same as the MO for 2b-BHLYP (LUMO+6), which is a sulfur-nitrogen _\pi^* and nitrogen-amide oxygen _\sigma^*_. The largest transition in the main peak is LUMO+14 which is a SC_\sigma^*_.

An initial look at the calculations for 4b-mPW1PW, Figure Figure 5.17b), yields a very promising match to the experimental spectrum. The main donors to the lower energy lineshape of the spectrum are LUMO and LUMO+6. Once more, the same electron distribution seen for 2b-BHLYP (LUMO+6), 4b-BHLYP (LUMO+7) occurs for 4b-mPW1PW in LUMO+6.

The calculations for 5b with BHLYP and mPW1PW are consistent with the previous assessments. The MOs in the energy range for the shoulder contribution for both BHLYP (LUMO+7) and mPW1PW (LUMO+5) are similar to each other and with 2b and 4b. The main absorption peak are equivalent SC_\sigma^* contributions for 5b-mPW1PW, 4b-BHLYP and 4b-mPW1PW; in 5b-BHLYP, this MO is a nitrogen-sulfur-oxygen _\sigma^* interaction. Figures Figure 5.22 and Figure 5.23 display the equivalent MOs for the shoulder transition.

A comparison of the bond lengths calculated for all sulfonamides and N-hydroxyl sulfonamides with BP86/TZVP (Figure Table 5.2, Table 5.3), BHLYP/def2-TZVP and mPW1PW/def2-TZVP levels of theory indicate small variations within each level of theory. For both the sulfonamide and N-hydroxy sulfonamide the sulfur-carbon bond exhibited a variation of 0.02Å through the range of Ham-
(a) Comparison of experimental and DFT simulated spectra of 2b.

(b) Calculated energy levels and electron density diagrams for the first six molecular orbitals of 2b.

**Figure 5.11:** BHLYP/def2-TZVP simulation of experimental S K-edge XAS spectrum of N-hydroxy benzenesulfonamide.
(a) Comparison of experimental and DFT simulated spectra of 2b.

(b) Calculated energy levels and electron density diagrams for the first six molecular orbitals of 2b.

**Figure 5.12:** mPW1PW/def2-TZVP simulation of experimental S K-edge XAS spectrum of N-hydroxy benzenesulfonamide.
Figure 5.13: MOs for 2b, with energy density diagrams for the MOs which may designate the shoulder for each functional: BP86, BLYP, and mPW1PW, as a sulfur-nitrogen interaction.

methyl substituent. The consistency in S-C bond length, with varying Hammett parameter, is echoed in the crystal structures. The predicted sulfur-nitrogen bond lengths exhibit a small contraction with increasing electron withdrawing character in both the sulfonamides and N-hydroxy sulfonamides; but not to the extent seen in the NOH crystal structures. The bond length that displayed the greatest variation in the crystal structures, the nitrogen-hydroxyl oxygen, varies the least in the calculations. Once again, this echoes the problems in predicting the lower edge XAS feature which arises with amide hydroxylation. For complete tables of all substituent predicted bond lengths at various levels of theory, see Appendix B.3.

The predicted bond distances of alkyl and aryl sulfonamides are not shown to differ greatly. According to the predictions for the sulfonamides, the R-group—be it alkyl, aryl, electron donating or electron withdrawing—seems to have a small impact on the overall bonding structure. However, in the case
(a) Comparison of 3a experimental and BHLYP/def2-TZVP simulated spectra.

(b) Comparison of 3a experimental and mPW1PW/def2-TZVP simulated spectra.

Figure 5.14: Experimental spectrum of p-Methoxybenzene sulfonamide (3a), in red, calculated XAS 3a spectra in dashed blue line.
(a) Comparison of 3b experimental and BHLYP/def2-TZVP simulated spectra.

(b) Comparison of 3b experimental and mPW1PW/def2-TZVP simulated spectra.

**Figure 5.15:** Experimental spectrum of N-hydroxy p-methoxybenzene sulfonamide (3b), in red, calculated 3b XAS spectra in dashed blue line.
(a) Comparison of 4a experimental and BHLYP/def2-TZVP simulated spectra.

(b) Comparison of 4a experimental and mPW1PW/def2-TZVP simulated spectra.

**Figure 5.16:** Experimental spectrum of p-Toluenebenzene sulfonamide (4a), in red, and calculated 4a XAS spectra in dashed blue line.
Figure 5.17: Experimental spectrum of N-hydroxy p-toluenebenzene sulfonamide (4b), in red, and calculated 4b XAS spectra in dashed blue line.

(a) Comparison of 4b experimental and BHLYP/def2-TZVP simulated spectra.

(b) Comparison of 4b experimental and mPW1PW/def2-TZVP simulated spectra.
(a) Comparison of 5a experimental and BHLYP/def2-TZVP simulated spectra.

(b) Comparison of 5a experimental and mPW1PW/def2-TZVP simulated spectra.

**Figure 5.18:** Experimental spectrum of p-Chlorobenzene sulfonamide (5a), in red, and calculated 5a XAS spectra in dashed blue line.
(a) Comparison of 5b experimental and BHLYP/def2-TZVP simulated spectra.

(b) Comparison of 5b experimental and mPW1PW/def2-TZVP simulated spectra.

**Figure 5.19:** Experimental spectrum of N-hydroxy p-chlorobenzene sulfonamide (5b), in red, and calculated 5b XAS spectra in dashed blue line.
(a) Comparison of 6a experimental and BHLYP/def2-TZVP simulated spectra.

(b) Comparison of 6a experimental and mPW1PW/def2-TZVP simulated spectra.

Figure 5.20: Experimental spectrum of p-Nitrobenzene sulfonamide (6a), in red, and calculated 6a XAS spectra in dashed blue line.
(a) Comparison of 6b experimental and BHLYP/def2-TZVP simulated spectra.

(b) Comparison of 6b experimental and mPW1PW/def2-TZVP simulated spectra.

**Figure 5.21:** Experimental spectrum of N-hydroxy p-nitrobenzene sulfonamide (6b), in red, and calculated 6b XAS spectra in dashed blue line.
Figure 5.22: MOs for 4b, with energy density diagrams for the MOs which may designate the shoulder for each functional: BP86, BHLYP and mPW1PW, as a sulfur-nitrogen interaction.
Figure 5.23: MOs for 5b, with energy density diagrams for the MOs which may designate the shoulder for each functional: BP86, BHLYP and mPW1PW, as a sulfur-nitrogen interaction.
Table 5.2: Experimental bond distances of sulfonamides calculated using BP86/TZVP level of theory.

<table>
<thead>
<tr>
<th>Bond Length (Å)</th>
<th>1a</th>
<th>3a</th>
<th>4a</th>
<th>2a</th>
<th>5a</th>
<th>6a</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-C</td>
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<td>1.807</td>
<td>1.813</td>
<td>1.817</td>
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Table 5.3: Experimental bond distances N-hydroxy sulfonamides calculated using BP86/TZVP level of theory.

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<tr>
<th>Bond Length (Å)</th>
<th>1b</th>
<th>3b</th>
<th>4b</th>
<th>2b</th>
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<tr>
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of the N-hydroxy alkylsulfonamide, both the sulfur-carbon and sulfur-nitrogen bond distance are elongated, compared to the N-hydroxy arylsulfonamides. Could this lead to the assumption that both the sulfur-carbon and the sulfur-nitrogen bonds are weaker for alkyl substitutions? If we apply the trends given in the aryl sulfonamides, to a view of the sulfur from the alkyl perspective, the elongation of the SC bond indicates an electron withdrawing nature of the methyl group; from the nitroxyl side of the sulfur, an electron donating nature. It is clear that the sulfone oxygens create areas of delocalized electron density which may stabilize this counterintuitive development. The NO bond length, again, shows little change within R-group variance; and it is likely that a better description of this electron rich area would allay the behavior seen in the simulations.

Hammett plots for the sulfur-nitrogen, sulfur-carbon and nitrogen-hydroxyl oxygen are show in Figures Figure 5.24. The calculations and assessments to follow will be using BP86/TZVP level of theory.
Figure 5.24: Hammett plots of sulfur-carbon bond lengths calculated at the BP86/TZVP vs. $\sigma_p, \sigma^+, \sigma^-$. 

(a) Sulfonamides.

(b) N-hydroxy sulfonamides.
Figure 5.25: Hammett plots of sulfur-nitrogen bond lengths calculated at the BP86/TZVP vs. $\sigma_p$, $\sigma_p^+$, $\sigma_R$.
Figure 5.26: Hammett plots of nitrogen-oxygen bond lengths at the BP86/TZVP level of N-Hydroxy sulfonamides vs. $\sigma_p, \sigma^+, \sigma^-$. The geometry predicted with BP86/TZVP gives rise to the following Hammett equations:

For the NOHS sulfur-carbon bond distances:

\[
\Delta S - C = 0.017 \sigma_p + 1.80 \quad R^2 = 0.813 \quad (5.1)
\]

\[
\Delta S - C = 0.013 \sigma^+ + 1.80 \quad R^2 = 0.961 \quad (5.2)
\]

\[
\Delta S - C = 0.044 \sigma^- + 1.81 \quad R^2 = 0.950 \quad (5.3)
\]

For the NOHS sulfur-nitrogen bond distances:

\[
\Delta S - N = -0.008 \sigma_p + 1.78 \quad R^2 = 0.951 \quad (5.4)
\]
\[ \Delta S - N = -0.006 \sigma^+ + 1.78 \quad R^2 = 0.980 \] (5.5)

\[ \Delta S - N = -0.020 \sigma^- + 1.78 \quad R^2 = 0.956 \] (5.6)

The best fit for both SC and SN bond distances once again occurs with \( \sigma^+ \). The trends for the SN agrees with that of the equations found for the NOHS crystal structure. The contraction of the sulfur-nitrogen bond with EWG is consistent with the idea that the bond is stabilized between two electron dense areas. This does not necessarily correlate to the strength of the bond. As seen in Scheme 4.2 this contraction could occur due to electrostatics, an EWG will destabilize this bond leading to cleavage of S-N.

### 5.2 Conclusion

The DFT calculations lead to very interesting results. The XAS spectra for the unsubstituted amide sulfonamide compounds were successfully simulated using BP86/TZVP level of theory. To recap, the XAS data for methanesulfonamide shows a single absorption peak, which corresponds to a \( \pi^- \) framework through the carbon-sulfur-nitrogen bonds. Experimentally, the introduction of an aryl group produced a shoulder (peak X), at approximately 2478eV, which computationally was shown to correspond to the sulfur-carbon \( \pi^- \). Upon amide hydroxylation of methane sulfonamide, a new feature emerges in the XAS at around 2477eV (peak Y), due to a perturbation in the nature of the sulfur-nitrogen bond. This feature is also seen in the aryl N-hydroxy sulfonamides, at similar energies; these aryl compounds present both a shoulder due to the SC\( \pi^- \) (peak X) and a peak due to sulfur-nitrogen interaction (peak Y). The simulated spectra for these N-hydroxy compounds, however, no longer faithfully reproduce the experimental data. The use of a variety of functionals and basis sets still fall short of explaining the peak at 2477eV. The experimental data clearly indicate that the hydroxyl substitution to the nitrogen has a far greater
impact on the sulfonamide moiety than the calculations suggest. Substituent effects also do not exhibit a large affect on the outcome of the simulated spectra regardless of functional, as seen in Figures Figure 5.27 and Figure 5.28. The only noticeable difference is a shift in the SC\(^{\pi}\) peak at 2477eV to approximately 0.5eV higher for the nitrobenzene species. This is somewhat consistent to the experimental data, where the greater differences are seen to occur with changes at the nitrogen as opposed to changes at the R-group.

Why is it, then, that with satisfactory descriptions of molecules like sulfonic acids and s-nitrosothiols are we no longer able to describe N-hydroxy sulfonamides and its seemingly small modification? An explanation could lie in the incongruity of predicting an excited state model, using a ground state calculation. X-ray absorption spectroscopy is an excited state description of a molecule while DFT is based on a ground state model. The application TD-DFT to excite the S1s core electron and the subsequent relaxation of the remaining electrons to fill said core hole may not accurately reflect the actual electronic structure of sulfonamides, and hence, would not accurately predict how the hydroxylation would affect its structure. There is also the possibility that the sulfur-nitrogen\(^{\pi}\), which appears at higher energy—at approximately 2480eV—represents the low energy peak but simply appears at the wrong energies in the calculations. Calculated transitions from the sulfur 1s to SC MOs and SN MOs would occur at similar energies and it is possible with BHL YP or mPW1PW functionals the SN transitions are overestimated and may in reality be lower.

We can arrive at the conclusion that regardless of the incomplete description of the sulfonamide moiety, a new perspective is revealed with the sulfur K-edge data. It is interesting to see that small modifications can have an such an impact not only on the XAS spectra but also on our ability to describe the electronic structure of sulfonamides using standard DFT methods. Undoubtedly, XAS/DFT of other small organic molecules will show some disparity or perhaps, even, suggest a better model from which the electronic structure of sulfonamides can be better understood.
Figure 5.27: BHLYP/def2-TZVP XAS spectra.
(a) Sulfonamides.

(b) N-hydroxy sulfonamides.

Figure 5.28: mPW1PW/def2-TZVP XAS spectra.
Chapter 6

Concluding Remarks and Future Directions

In this thesis, the electronic structure of sulfonamides and its affects on the sulfur-nitrogen bond have been investigated. Factors that govern transmission effects through this bond are important in understanding the sulfur-nitrogen bond, which is a crucial aspect in determining NO and HNO release. Various modifications to the sulfonamide moiety have illustrated that small changes can lead to large perturbations in the electronic distribution of the molecule. The use of sulfur K-edge x-ray absorption spectroscopy has allowed a unique view of the outcomes of these modifications on the sulfur atom and, hence, the sulfur-nitrogen bond.

In Chapter three the effect of changes in R-group and oxidation state on the sulfonamide moiety were explored. XAS data show that each addition of oxygen shifts the sulfur $Z_{eff}$ to higher energies. Methanesulfonamide and tert-butyl sulfinate exhibit similarly shaped absorption peaks, each with a single main absorption peak. DFT calculations show that the LUMO for both are a mixed sulfur-nitrogen-sulfone oxygen $\pi^*$ framework. The alteration of an alkyl R-group to an aryl substituent, as in benzene sulfonamide, displays an additional low energy shoulder to the main absorption peak. This shoulder was confirmed via DFT as the sulfur-carbon $\pi^*$. DFT calculations of sulfonated amides also indicate a more delocalized sigma framework with each addition of oxygen which
is consistent with the idea that, as a functional group the sulfinamido group is least electron withdrawing of carbonyl compounds, sulfones and sulfonate esters.\textsuperscript{10}

Chapter four investigates modifications of the sulfonamide R-group with Hammett parameters. Substituent effects do not exhibit a straight-forward trend in the N-hydroxy sulfonamide and parent sulfonamide XAS spectra; where the changes in the R-group are largely overshadowed by the amide hydroxylation, further cementing the complex nature of the sulfonamide moiety. To further parse the effects of these modifications, more traditional spectroscopic techniques were used in conjunction with quantitative structure activity relationships. QSAR studies showed NMR and x-ray crystallographic data correlated well with Hammett parameters and that for the sulfonamide nitrogen, electron-withdrawing groups would lead to a more positive nitrogen. The bond length data trend is also supported by Sirsalmath \textit{et al.},\textsuperscript{29} where substituents with EWG groups have shorter NO bond lengths, and is interpreted to mean that a shorter NO bond length would facilitate the formation of HNO, which would destabilize the sulfur-nitrogen bond. IR stretching frequencies for sulfonamides blueshifted upon hydroxylation for the $\nu$ sulfur-nitrogen and $\nu$nitrogen-oxygen stretching frequencies; however, the most redshifted of these were the electron-withdrawing substituents for the N-hydroxy sulfonamides, again pointing to a destabilization of the S-N bond. Mainly, substituent effects by R-group were mostly inductive with some potential for stabilization by resonance, yet substitutions at the amide had a far larger impact on the QSAR and XAS studies.

In Chapter five DFT calculations of the sulfonamides and N-hydroxy sulfonamides, used in Chapter four, were carried out to further examine and simulate the XAS spectra. For the parent sulfonamides, reasonable DFT estimates and spectral simulations were achieved. DFT calculations fell short, however, when reproducing the lower edge XAS feature which arises upon amide hydroxylation. A thorough test of various functionals and basis sets resulted in the selection of mPW1PW and BHL YP as functionals to be used for the XAS simulation of sulfonamides. The low energy feature was still not faithfully reproduced, but the simulated spectra were much more closely emulated. It is possible that the calculated transition energies for SC$_{\alpha^*}$ and SN$_{\alpha^*}$ are very close and the
functionals may transpose the energies for these two transitions.

It has been shown that bacteriostatic activity in sulfonamides are very dependent on variations of the N atom of the sulfonamido group.\textsuperscript{41,76} We have seen that an alteration from a proton to a hydroxyl group pulls electron density away from the nitrogen perturbing the bond between the sulfur and nitrogen. Immediate future work will center on exploring how further substitutions on the amide, see Figure 6.1, will affect the sulfonamido moiety. XAS data has been acquired and initial data analysis indicates that a methoxy substituent on the amide nitrogen has a similar effect as the hydroxyl substituent on the XAS spectra; whereas, phenyl or methyl substitution does not exhibit the lower energy peak Y. QSAR and DFT calculations will be undertaken to further investigate these modifications.

Though this body of work has focused on utilizing XAS for sulfonamides as small organic molecules, the use of sulfonamides as ligands to metal centers would allow a glimpse of these molecules in a different electronic environment. Further work on nitric oxide and azanone release could be based on using sulfonamides as ligands for coordination to metal centers. For example, biologically some tissues contain both HNO and NO. As the two species exhibit different behavior biochemically in vasodilation processes, a selective trap for one will enable the other to complete its dilatory function. Ferric porphyrins with N-hydroxy sulfonamide ligands have been shown to trap NO, yielding ferrous nitrosyl compounds.\textsuperscript{103} Mn(III) porphyrins with N-hydroxy sulfonamide ligands, on the other hand, have been shown to trap HNO.\textsuperscript{104} The selectivity of NO and HNO to the different metal centered porphyrins would be an interesting candidate for metal-sulfur ligand XAS.

Another interesting line of sulfonamide research would be in the structure-activity of carbonic anhydrase. Carbonic anhydrase (CA) is a well studied zinc metalloenzyme which is strongly inhibited when bound to sulfonamides. There are an array of CA isozymes in a plethora of tissue and cells, but there are few specific isozyme inhibitors.\textsuperscript{15,105} CA inhibitors can be prone to side-effects when used as drugs so specificity of inhibition would greatly enhance the use of sulfonamides as drugs. The use of metal-sulfonamide ligand XAS and DFT could explain how CAs bind so strongly to the sulfonamides by revealing the
Figure 6.1: Amide substitutions and S K-edge XAS spectra of Benzenesulfonamide (—), N-CH$_3$ Benzenesulfonamide (—), N-Ph Benzenesulfonamide (—), N-OH Benzenesulfonamide (—) and N-OCH$_3$ Benzenesulfonamide (—).
electronic framework. Subsequent work could then be focused on enhancing specific aspects of this Zn(II)-sulfonamide bond to target inhibition of specific isozymes.

Overall, this thesis has shown that S K-edge XAS has proven a very effective tool for the study of small molecules. We have found evidence for an interesting electronic structure for sulfonamides which has not been seen with other methods of analysis. The low energy peak found in the XAS data of the N-hydroxy sulfonamides point to the fact that the degree of $SN_{\pi^*}$ character is highly dependent on the nature of substituents on nitrogen, providing a possible avenue for controlling the strength of the SN bond. Along with XAS and DFT, QSAR studies have given some insight to the intramolecular structure of sulfonamides. It has been shown that in sulfonamides electron-withdrawing groups destabilize the sulfur-nitrogen bond, yet, EWG have a stabilizing affect on the sulfur-nitrogen bond when the amide is hydroxylated. While we do not yet have a complete picture of what governs intramolecular behavior, we have found new avenues to explore and further experiments to undertake. The methods used in this thesis can easily be applied to other sulfur-based organic systems, or indeed, organic systems in general.
Bibliography


Appendix A

Experimental Data

A.1 $^1$H NMR

![Figure A.1: $^1$H NMR spectrum of methanesulfonamide (1a)](image-url)
Figure A.2: $^1$H NMR spectrum of N-hydroxy methanesulfonamide (1b)
Figure A.3: $^1$H NMR spectrum of benzenesulfonamide (2a)
Figure A.4: $^1$H NMR spectrum of N-hydroxy benzenesulfonamide (2b)
Figure A.5: $^1$H NMR spectrum of p-methoxybenzene sulfonamide (3a)
Figure A.6: $^1$H NMR spectrum of N-hydroxy p-methoxybenzenesulfonamide (3b)
**Figure A.7:** $^1$H NMR spectrum of p-toluene sulfonamide (4a)
Figure A.8: $^1$HNMR spectrum of N-hydroxy p-toluene sulfonamide (4b)
Figure A.9: $^1$H NMR spectrum of p-chlorobenzene sulfonamide (5a)
Figure A.10: $^1$H NMR spectrum of N-hydroxy p-chlorobenzene sulfonamide (5b)
Figure A.11: $^1$H NMR spectrum of p-nitrobenzene sulfonamide (6a)
Figure A.12: $^1$H NMR spectrum of N-hydroxy p-nitrobenzene sulfonamide (6b)
Figure A.13: IR spectra of methanesulfonamide (blue) and N-hydroxy methanesulfonamide (red).
Figure A.14: IR spectra of benzenesulfonamide (blue) and N-hydroxy benzenesulfonamide (red).
Figure A.15: IR spectra of p-methoxybenzenesulfonamide (blue) and N-hydroxy p-methoxybenzenesulfonamide (red).
Figure A.16: IR spectra of toluenesulfonamide (blue) and N-hydroxy toluenesulfonamide (red).
Figure A.17: IR spectra of p-chlorobenzenesulfonamide (blue) and N-hydroxy p-chlorobenzenesulfonamide (red).
Figure A.18: IR spectra of p-nitrobenzenesulfonamide (blue) and N-hydroxy p-nitrobenzenesulfonamide (red).
### A.3 Selected Crystallographic Data

**Table A.1:** Selected crystallographic data for compounds 2b, 3b and 6b.

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Appendix B

Calculated Data
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*Figure B.1:* Calculated bond lengths of N-hydroxy benzenesulfonamide using sundry functionals and basis sets.
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<td>D ZORA</td>
<td>1.783</td>
<td>1.684</td>
<td>1.429</td>
<td>1.414</td>
<td>1.783</td>
<td>1.684</td>
<td>1.429</td>
<td>1.414</td>
<td>1.783</td>
<td>1.684</td>
<td>1.429</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure B.2:** Calculated bond lengths of N-hydroxy benzenesulfonamide using relativistic effects (ZORA) in conjunction to sundry functionals and basis sets.
B.2 Comparison of S K-Edge Spectrum Simulation

Figure B.3: Comparison of methane sulfonamide experimental data with calculated data; BP86, BLYP, and mPW1PW
Figure B.4: Comparison of NOH- methane sulfonamide experimental data with calculated data; BP86, BLYP, and mPW1PW
Figure B.5: Comparison of benzene sulfonamide experimental data with calculated data; BP86, BHLYP, and mPW1PW
Figure B.6: Comparison of NOH- benzenesulfonamide experimental data with calculated data; BP86, BHLYP, and mPW1PW
Figure B.7: Comparison of p-methoxybenzene sulfonamide experimental data with calculated data; BP86, BHLYP, and mPW1PW
Figure B.8: Comparison of NOH-p- methoxybenzene sulfonamide experimental data with calculated data; BP86, BHLYP, and mPW1PW
Figure B.9: Comparison of toluene sulfonamide experimental data with calculated data; BP86, BHLYP, and mPW1PW
Figure B.10: Comparison of NOH-toluene sulfonamide experimental data with calculated data; BP86, BHLYP, and mPW1PW
Figure B.11: Comparison of p-chlorobenzene sulfonamide experimental data with calculated data; BP86, BHLYP, and mPW1PW
Figure B.12: Comparison of NOH-p- chlorobenzene sulfonamide experimental data with calculated data; BP86, BHLYP, and mPW1PW
Figure B.13: Comparison of p-nitrobenzene sulfonamide experimental data with calculated data; BP86, BHLYP, and mPW1PW.
Figure B.14: Comparison of NOH-p- nitrobenzene sulfonamide experimental data with calculated data; BP86, BHLYP, and mPW1PW
B.3  DFT Bond Distances for Sulfonamide Compounds

**Table B.1:** Experimental bond distances of sulfonamides calculated using BP86/TZVP level of theory.

<table>
<thead>
<tr>
<th>Bond Length (Å)</th>
<th>1a</th>
<th>3a</th>
<th>4a</th>
<th>2a</th>
<th>5a</th>
<th>6a</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-C</td>
<td>1.817</td>
<td>1.807</td>
<td>1.813</td>
<td>1.817</td>
<td>1.815</td>
<td>1.832</td>
</tr>
<tr>
<td>S-N</td>
<td>1.729</td>
<td>1.733</td>
<td>1.729</td>
<td>1.726</td>
<td>1.724</td>
<td>1.704</td>
</tr>
<tr>
<td>S-O</td>
<td>1.487</td>
<td>1.490</td>
<td>1.489</td>
<td>1.488</td>
<td>1.488</td>
<td>1.481</td>
</tr>
<tr>
<td>S-O</td>
<td>1.487</td>
<td>1.487</td>
<td>1.488</td>
<td>1.488</td>
<td>1.487</td>
<td>1.481</td>
</tr>
</tbody>
</table>

**Table B.2:** Experimental bond distances N-hydroxy sulfonamides calculated using BP86/TZVP level of theory.

<table>
<thead>
<tr>
<th>Bond Length (Å)</th>
<th>1b</th>
<th>3b</th>
<th>4b</th>
<th>2b</th>
<th>5b</th>
<th>6b</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-C</td>
<td>1.821</td>
<td>1.793</td>
<td>1.801</td>
<td>1.806</td>
<td>1.804</td>
<td>1.814</td>
</tr>
<tr>
<td>S-N</td>
<td>1.804</td>
<td>1.784</td>
<td>1.781</td>
<td>1.780</td>
<td>1.778</td>
<td>1.775</td>
</tr>
<tr>
<td>S-O</td>
<td>1.478</td>
<td>1.487</td>
<td>1.487</td>
<td>1.487</td>
<td>1.486</td>
<td>1.485</td>
</tr>
<tr>
<td>S-O</td>
<td>1.497</td>
<td>1.497</td>
<td>1.496</td>
<td>1.495</td>
<td>1.494</td>
<td>1.492</td>
</tr>
<tr>
<td>N-O</td>
<td>1.422</td>
<td>1.425</td>
<td>1.425</td>
<td>1.424</td>
<td>1.423</td>
<td>1.420</td>
</tr>
</tbody>
</table>

**Table B.3:** Experimental bond distances of sulfonamides calculated using BLYP/Def2-TZVP level of theory.

<table>
<thead>
<tr>
<th>Bond Length (Å)</th>
<th>1a</th>
<th>3a</th>
<th>4a</th>
<th>2a</th>
<th>5a</th>
<th>6a</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-C</td>
<td>1.757</td>
<td>1.751</td>
<td>1.756</td>
<td>1.760</td>
<td>1.759</td>
<td>1.772</td>
</tr>
<tr>
<td>S-N</td>
<td>1.635</td>
<td>1.636</td>
<td>1.634</td>
<td>1.632</td>
<td>1.631</td>
<td>1.616</td>
</tr>
<tr>
<td>S-O</td>
<td>1.419</td>
<td>1.420</td>
<td>1.419</td>
<td>1.419</td>
<td>1.418</td>
<td>1.414</td>
</tr>
<tr>
<td>S-O</td>
<td>1.419</td>
<td>1.420</td>
<td>1.419</td>
<td>1.419</td>
<td>1.418</td>
<td>1.414</td>
</tr>
</tbody>
</table>
**Table B.4:** Experimental bond distances N-hydroxy sulfonamides calculated using BHL YP/Def2-TZVP level of theory.

<table>
<thead>
<tr>
<th>Bond Length (Å)</th>
<th>1b</th>
<th>3b</th>
<th>4b</th>
<th>2b</th>
<th>5b</th>
<th>6b</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-C</td>
<td>1.756</td>
<td>1.739</td>
<td>1.745</td>
<td>1.749</td>
<td>1.748</td>
<td>1.757</td>
</tr>
<tr>
<td>S-N</td>
<td>1.676</td>
<td>1.663</td>
<td>1.661</td>
<td>1.660</td>
<td>1.658</td>
<td>1.654</td>
</tr>
<tr>
<td>S-O</td>
<td>1.412</td>
<td>1.418</td>
<td>1.417</td>
<td>1.417</td>
<td>1.417</td>
<td>1.415</td>
</tr>
<tr>
<td>S-O</td>
<td>1.425</td>
<td>1.424</td>
<td>1.424</td>
<td>1.423</td>
<td>1.422</td>
<td>1.420</td>
</tr>
<tr>
<td>N-O</td>
<td>1.389</td>
<td>1.384</td>
<td>1.384</td>
<td>1.384</td>
<td>1.383</td>
<td>1.381</td>
</tr>
</tbody>
</table>

**Table B.5:** Experimental bond distances of sulfonamides calculated using mPW1PW/Def2-TZVP level of theory.

<table>
<thead>
<tr>
<th>Bond Length (Å)</th>
<th>1a</th>
<th>3a</th>
<th>4a</th>
<th>2a</th>
<th>5a</th>
<th>6a</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-C</td>
<td>1.765</td>
<td>1.758</td>
<td>1.763</td>
<td>1.768</td>
<td>1.766</td>
<td>1.779</td>
</tr>
<tr>
<td>S-N</td>
<td>1.649</td>
<td>1.650</td>
<td>1.648</td>
<td>1.646</td>
<td>1.644</td>
<td>1.631</td>
</tr>
<tr>
<td>S-O</td>
<td>1.431</td>
<td>1.432</td>
<td>1.431</td>
<td>1.431</td>
<td>1.430</td>
<td>1.426</td>
</tr>
<tr>
<td>S-O</td>
<td>1.431</td>
<td>1.432</td>
<td>1.431</td>
<td>1.431</td>
<td>1.430</td>
<td>1.426</td>
</tr>
</tbody>
</table>

**Table B.6:** Experimental bond distances N-hydroxy sulfonamides calculated using mPW1PW/Def2-TZVP level of theory.

<table>
<thead>
<tr>
<th>Bond Length (Å)</th>
<th>1b</th>
<th>3b</th>
<th>4b</th>
<th>2b</th>
<th>5b</th>
<th>6b</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-C</td>
<td>1.764</td>
<td>1.746</td>
<td>1.752</td>
<td>1.756</td>
<td>1.755</td>
<td>1.764</td>
</tr>
<tr>
<td>S-N</td>
<td>1.695</td>
<td>1.679</td>
<td>1.677</td>
<td>1.676</td>
<td>1.674</td>
<td>1.669</td>
</tr>
<tr>
<td>S-O</td>
<td>1.424</td>
<td>1.430</td>
<td>1.430</td>
<td>1.429</td>
<td>1.429</td>
<td>1.428</td>
</tr>
<tr>
<td>S-O</td>
<td>1.439</td>
<td>1.438</td>
<td>1.437</td>
<td>1.436</td>
<td>1.436</td>
<td>1.434</td>
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<tr>
<td>N-O</td>
<td>1.397</td>
<td>1.393</td>
<td>1.393</td>
<td>1.392</td>
<td>1.392</td>
<td>1.390</td>
</tr>
</tbody>
</table>

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Appendix C

DFT input files

C.1 Selected ORCA Input Files

#2a, benzenesulfonamide

#Geometry optimization
! UKS BP86 RI TZVP TightSCF SlowConv SCFConv7 OPT NumFreq
*xyz 0 1
  S  -0.120179   1.583225  -0.173336
  N  -0.004535   1.540635  -1.894918
  O   1.217804   1.222062   0.370497
  O  -0.821307   2.849209   0.173753
  C  -1.250781   0.208274   0.194786
  C  -0.717309  -1.054805   0.458683
  C  -1.592332  -2.106312   0.745858
  C  -2.973371  -1.884647   0.773721
  C  -3.487836  -0.608183   0.519113
  C  -2.625339   0.452170   0.228519
  H  -0.286265   2.455532  -2.256584
  H   0.962827   1.328791  -2.152212
  H   0.363226  -1.202579   0.452272
  H  -1.191675  -3.098742   0.958182
  H  -3.651604  -2.708506  1.002341
  H  -4.564602  -0.433207   0.554824
  H  -3.005960   1.457083   0.044500
*

$new_job
! UKS BP86 RI TZVP TightSCF SlowConv SCFConv7
%base "2a_xes"
%xes Coreorb 0,0
OrbOp 0,1
end
*xyzfile 0 1 2a.xyz

$new_job
! UKS BP86 RI TZVP TightSCF SlowConv SCFConv7
%base "2a_tddft"
%tddft OrbWin[0] = 0,0,-1,-1
OrbWin[1] = 0,0,-1,-1
nroots 200
maxdim 40000
triplets true
DoQuad true
end
*xyzfile 0 1 2a.xyz

!normalprint
!grid4 nofinalgrid

#2a, benzenesulfonamide

! UKS BHLYP NORI Def2-TZVP TightSCF SlowConv SCFConv7 OPT

*xyz 0 1
  S  -0.120179  1.583225  -0.173336
  N  -0.004535  1.540635  -1.894918
  O   1.217804  1.222062   0.370497
  O  -0.821307  2.849209   0.173753
  C  -1.250781  0.208274   0.194786
  C  -0.717309  -1.054805   0.458683
  C  -1.592332  -2.106312   0.745858
  C  -2.973371  -1.884647   0.773721
  C  -3.487836  -0.608183   0.519113
  C  -2.625339   0.452170   0.228519
  H  -0.286265   2.455532  -2.256584
  H   0.962827   1.328791  -2.152212
  H   0.363226  -1.202579   0.452272
  H  -1.191675  -3.098742   0.958182
  H  -3.651604  -2.708506   1.002341
  H  -4.564602  -0.433207   0.554824
  H  -3.005960   1.457083   0.044500
*

#XES
! UKS BHLYP NORI Def2-TZVP TightSCF SlowConv SCFConv7
%base "xes_2abh"
%xes Coreorb 0,0
OrbOp 0,1
end
*xyzfile 0 1 2a_bhlyp.xyz

#TDDFT
! UKS BHLYP NORI Def2-TZVP TightSCF SlowConv SCFConv7
%base "tddft_2abh"
%tddft OrbWin[0] = 0,0,-1,-1
OrbWin[1] = 0,0,-1,-1
nroots 200
  maxdim 40000
  triplets true
  DoQuad true
end
*xyzfile 0 1 2a_bhlyp.xyz

#peripheral information
!normalprint
!grid4 nofinalgrid

#2a, benzenesulfonamide
! UKS mPW1PW NORI Def2-TZVP TightSCF SlowConv SCFConv7 OPT

*xyz 0 1
S  -0.120179   1.583225  -0.173336
N  -0.004535   1.540635  -1.894918
O   1.217804   1.222062   0.370497
O  -0.821307   2.849209   0.173753
C  -1.250781   0.208274   0.194786
C  -0.717309  -1.054805   0.458683
C  -1.592332  -2.106312   0.745858
C  -2.973371  -1.884647   0.773721
C  -3.487836  -0.608183   0.519113
C  -2.625339   0.452170   0.228519
H  -0.286265   2.455532  -2.256584
H   0.962827   1.328791  -2.152212
H   0.363226  -1.202579   0.452272
H  -1.191675  -3.098742   0.958182
H  -3.651604  -2.708506  1.002341
H  -4.564602  -0.433207   0.554824
H  -3.005960   1.457083   0.044500
*
#XES
! UKS mPW1PW NORTI Def2-TZVP TightSCF SlowConv SCFConv7
%base "xes_2ampw"
%xes  Coreorb 0,0
       OrbDp 0,1
end
*xyzfile 0 1 2a_mpw.xyz

#TDDFT
! UKS mPW1PW NORTI Def2-TZVP TightSCF SlowConv SCFConv7
%base "tddft_2ampw"
%tddft OrbWin[0] = 0,0,-1,-1
       OrbWin[1] = 0,0,-1,-1
nroots 200
maxdim 40000
triplets true
DoQuad true
end
*xyzfile 0 1 2a_mpw.xyz

#peripheral information
!normalprint
!grid4 nofinalgrid

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