The nature of S-N bonding in sulfonamides and related compounds: insights into π-bonding contributions from Sulfur K-edge XAS

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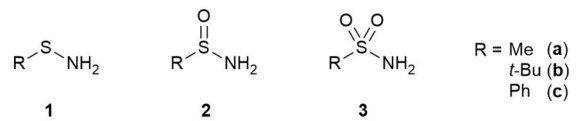
ABSTRACT: Molecules containing sulfur-nitrogen bonds, like sulfonamides, have long been of interest due to their many uses and chemical properties. Understanding the factors that cause sulfonamide reactivity is important, yet their continues to be controversy regarding the relevance of S-N π bonding in describing these species. In this paper, we use sulfur K-edge x-ray absorption spectroscopy (XAS) in conjunction with density functional theory (DFT) to explore the role of S_{3p} contributions to π-bonding in sulfonamides, sulfinamides and sulfenamides. We explore the nature of electron distribution of the sulfur atom and its nearest neighbors and extend the scope to explore the effects on rotational barriers along the sulfur-nitrogen axis. The experimental XAS data together with TD-DFT calculations confirm that sulfonamides, and the other sulfinated amides in this series, have essentially no S-N π bonding involving S_{3p} contributions and that electron repulsion and is the dominant force that affect rotational barriers.

Introduction

Sulfonamides (**3**) and their more reduced congeners (Scheme 1: sulfinamides, **2**, and sulfenamides, **1**) are common motifs in synthetic (1) (2) and pharmaceutical (3) (4) (5) chemistry. Their geometric and electronic properties seem particularly well suited for use in biological applications. Some of their fundamental properties – most notably the nature of the S-N bond in such species – have been hotly debated with a particular emphasis on the relevance and importance of π-type interactions to the S-N bond and the specific nature of such contributions (6) (7).

Scheme 1: Compounds discussed in this study, including methyl (a), t-butyl (b), and phenyl (c); sulfenamides (1), sulfinamides (2) and sulfonamides (3).



The extent of π contributions in the S-N bond of 1-3 has attracted particular attention, often with a focus on the thermodynamics and kinetics of both nitrogen inversion and rotational barriers about the S-N bond. Many studies have centered on these issues but a consensus regarding the role of π SN bonding in such systems has been elusive. For example, low rotational barriers - with concurrent large barriers to nitrogen inversion - in hydroquinolones have been used to argue that sterics are dominant and that π SN bonding is, at best, very weak in these systems.(6) By contrast, large rotational barriers in sulfenamides have been attributed to π SN bonding (specifically d-p π bonding); whereas these contributions are thought to be less significant in the corresponding sulfinamide and sulfonamide moieties, which exhibit lower rotational barriers.(8) Meanwhile, N,N-diisopropyl-nonafluorobutane-1-sulfonamide exhibits a substantial rotational barrier, due to the strongly electron-withdrawing nature of the fluorinated substituent which is interpreted as increased S-N π overlap.(9) By contrast, substituted hexahydropyrrolo[2,3-b]indole sulfonamides have a reduced rotational barrier, presumably due to the strongly electron-donating para-methoxy substitution.(10) NMR studies of arylsulfonamides

have shown little conjugation between the sulfur atom and the phenyl ring but indicate potential S-N π bonding.(11) The properties of these systems have also been interpreted by invoking negative hyperconjugation as has been postulated in other X_3AY species such as O_3ClF and F_3SN.(7) Most notably, however, direct measurements to probe the degree of π bonding in such systems have not been reported.

We have previously shown that Sulfur K-edge X-ray Absorption Spectroscopy (S K-edge XAS) can be used as a direct probe of bonding in organosulfur species. The degree of π- bonding in S-nitrosothiols (RSNO) was shown in a clearly observable formal SN $\pi^*\leftarrow S_{1s}$ pre-edge transition supported by quantitatively determining the S_{3p} contributions.(12) (13) In particular, S K-edge XAS is selective for S_{3p} contributions to π-bonding in RSNO-type systems. The experimentally determined nature of the SN bond in S-nitrosothiols is also in good agreement with detailed computational studies on these species.(14) Herein, we investigate the electronic structure of sulfenato, sulfinato and sulfonato amide species using S K-edge XAS with complementary density functional theory (DFT) calculations. Our focus is specifically on defining the nature of the S-N bond and the impact of π_{SN} bonding.

Results

Sulfur K-edge XAS data were successfully obtained for three of the target compounds: **3a**, **2b**, and **3c** (see Figure 1A). Rapid X-ray photodegradation was observed for related compounds under the conditions of the experiments and cryoprotection was insufficient to prevent photoreduction; a limited number of experimental data are therefore available. The scope of the series was increased by computationally exploring the remainder of the compounds in Scheme 1. The intense characteristic 'white line' feature (dominated by $\sigma^*_{SX}\leftarrow S_{1s}$ contributions) occurs at 2477 eV for **2b** and about 4 eV higher in energy for the more oxidized **3a** and **3c**. This energy shift is similar to observed changes between sulfinates and sulfonates(15) reflecting an increased Z_{eff} upon oxygenation. (16) The aryl sulfonate exhibits a low-energy shoulder (at 2479.4 eV) which is not present in the spectra of the alkyl species. This is consistent with similar features observed in aryl sulfonyl chlorides, which has previously been attributed to excited-state hyperconjugation with the aryl ring. (17) A weak feature visible at 2473 eV due to photoreduction is observded for **2b**. (18)

Time-dependent density functional theory (TD-DFT) calculations were performed on the complete series of compounds in Scheme 1, both for comparison with available experimental data and to further explore the rest of the series. The simulated S K-edge XAS spectra yield overall good agreement with the experimental data (see Figure 1B).

For methanesulfonamide, **3a**, the lowest energy final states are dominated by σ* contributions. Each of these final states fall into a narrow energy range leading to a single, intense feature corresponding to the white line in the S K-edge spectrum (see SI1). A more detailed analysis of the TD-DFT states reveal weak contributions from π^*_{SN} final states at similar energies to contributions from σ-type final states (see SI7-15), indicating mixed σ/π interactions from hyperconjugation. Such contributions are unresolvable in the experimental data and their contribution cannot be independently quantified experimentally. However, the lack of clearly discernible lower energy features in the spectrum, where π interactions would be expected, further indicate that direct S_{3p} contributions to π bonding are either not present or very weak.

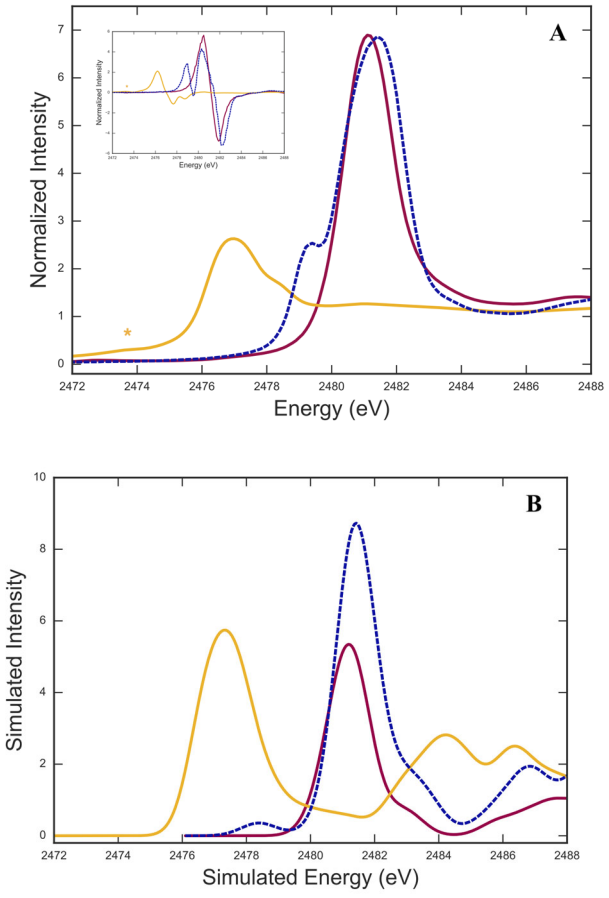


Figure 1: S K-edge XAS spectra (**A**) and their first-derivatives (**A**, inset) for compounds tertbutanesulfinamide (**2b**), methanesulfonamide (**3a**), and benzenesulfonamide (**3c**). A very weak feature (labeled with *) is observable in the pre-edge region for **2b** due to photoreduction in the beam. Spectra

have not been corrected for self-absorption effects. The TD-DFT simulated S K-edge XAS spectra (**B**) of tertbutanesulfinamide (**2b**), methanesulfonamide (**3a**), and benzenesulfonamide (**3c**). Overall simulated spectra are obtained by systematic broadening of all calculated transitions using a Gaussian lineshape with 1.3 eV FWHM, a reasonable approximation to that observed experimentally. Calculated final state energies for XAS simulations are also systematically shifted by +76 eV to offer better agreement with the experimental spectra (19).

Aryl substituents on the sulfonamide moiety (e.g., **3c**) have a significant impact on the S K-edge XAS spectra --- with the appearance of a relatively intense low-energy shoulder. Such a shoulder has also been observed in aryl sulfonyl chlorides (17) (as compared to their alkyl analogues) and reflects excited-state hyperconjugation with empty low-lying π* states from the aryl ring. The poor agreement in the intensity of this shoulder likely reflects both self-absorption effects in the data and the limited ability of TD-DFT calculations to account for large electronic relaxation effects in the final states. Aside from this shoulder feature, contributions to the rest of spectra are very similar to **3a** (see SI2).

In the case of sulfinamides (e.g., **2b**), a large shift to lower energies and an overall drop in the intensity of the edge features is observed. Both of these effects correlate with a decrease in Z_{eff}, which together lower the energy of the core-level transitions and decreases the oscillator strength of $S_{3p} \leftarrow S_{1s}$ transitions. (19) The distribution of final states is very similar to those obtained for the alkylsulfonamide, with dominant contributions from σ* final states and only minimal π* contributions through hyperconjugation.

TD-DFT results for S_{1s} excitation in the complete series of compounds listed in Scheme 1 reveal additional trends depending on the oxidation state of the sulfur as well as the nature of the substituents (alkyl vs. aryl). Visual representations of these comparisons are given in SI4, SI5, SI6. Most notably, the white line feature that represents both σ* contributions and hyperconjugative π* contributions broaden from $RSO_2NH_2 \rightarrow RSONH_2 \rightarrow RSNH_2$. As a consequence of this effect, contributions to the S-N bond from hyperconjugation are predicted to decrease with deoxygenation due to poorer energy matching of the final states. The energy of the predicted excited-state hyperconjugation feature in the aryl species is well separated from the white line feature in the most oxidized species but is expected to merge with the white line in the more reduced sulfenamides, see SI6b.

Further computational studies on each of these S-N containing species were performed to estimate rotational barriers about the S-N bond (ΔE^{rot}_{SN}), Table 1. There is surprisingly little difference between the rotational barriers as a function of the R substituent, in agreement with suggestions that sterics do not play a critical role in defining $\Delta Erot_{SN}$. (9) (20) Oxidation at the sulfur centre has an overall greater impact on rotational barriers, particularly in the sulfonamides, which exhibit the lowest $\Delta Erot_{SN}$.

Table 1: Calculated rotational energies about the S-N bond.

R	ΔE^{rot}_{SN} *kJ/mol*		
	$RSNH_2$	$RSONH_2$	RSO_2NH_2
CH_3	25.2	26.4	14.8
$C(CH_3)_3$	29.1	22.9	16.6
C_6H_5	30.1	26.4	14.3
average	28.1 ± 2.6	25.2 ± 2.0	15.2 ± 1.2

Discussion

S K-edge XAS provides an opportunity to evaluate potential π contributions to bonding in S-N containing species. Given the atomic selection rules that generally govern core spectroscopy, S K-edge XAS is particularly selective to S_{3p} final state contributions and thus provides a direct experimental probe of contributions to bonding from valence *p* states. The data we have collected are readily supported by TDDFT calculations, allowing us to explore the broader implications of our results. Our experimental XAS data as well as TD-DFT calculations confirm that sulfonamides, sulfinamides, and sulfenamides have essentially no S-N π bonding involving S_{3p} contributions. Mulliken population analysis and electron density distributions in the x-ray final states (corresponding to the lowest-unoccupied states) also indicate no π contributions to bonding (see SI4b, SI5b, SI6b). The only notable exception is the presence of significant sulfur-carbon π_{SC} contributions in the lowest-energy final states for species with aryl substitution (**1c**, **2c**, and **3c**). This π delocalization into the phenyl ring is analogous to that which has been observed in other aryl sulfonyl species and is an excited state phenomenon. $RS(O)_nNH_2$ moieties show no spectroscopic evidence of S_{3p} contributions to π bonding in any of the investigated species.

As has been previously noted, (8) (20) the rotational barriers along the S-N axis differ markedly as a function of the oxidation state of the sulfur atom. We have, therefore, further explored the nature of the rotational barrier in these species, in greater detail, using DFT calculations. The calculated energies indicate an increase in barriers to rotation upon deoxygenation of the sulfur atom for all R-groups, Table 1, although these are small in all cases. The

geometry at the minimum energy for all sulfenamide species occurs around the 60° H-N-S-C dihedral angle, where the nitrogen lone pair is anti to the sulfur-R-group bond, Figure 2. At maximum energy the nitrogen lone pair is eclipsed with one of the sulfur lone pairs. Similarly, for the sulfonamide species, the minimum occurs when the nitrogen lone pair is anti to the R- group and the sulfur-oxygen bonds are gauche to the amide hydrogens. Both the sulfinamide and sulfonamide maximum energy configurations are similar to the eclipsed structure of the sulfenamides. A slight difference in configuration is seen at the sulfinamide minimum, where the R-group is gauche and the S-O bond is anti to the nitrogen lone pair, respectively.

Comparisons of the SN electronic and geometric descriptions at both maximum and minimum energy geometries show relatively small differences. The largest effect is observed in the S-N bond distances, which elongate by ~6pm in the sulfenamides during bond rotation. This elongation is smaller for the sulfinamides (~4pm) and even shorter for the sulfonamides (~2pm). These structural differences do not reflect any substantial differences in SN bonding in different conformers. We find only very small electron density changes during rotation, suggesting that the nature of the bond is not affected, SI Table 1, and thus implying little to no π contributions in this bond. Taken together, our results support previous proposals that rotational barriers are dominated by electron repulsion. We note that experimental validation of the lack of d-p π interactions cannot be offered based on S K-edge studies and we are currently exploring the use of S L-edge spectroscopy to address this specific point with greater clarity.

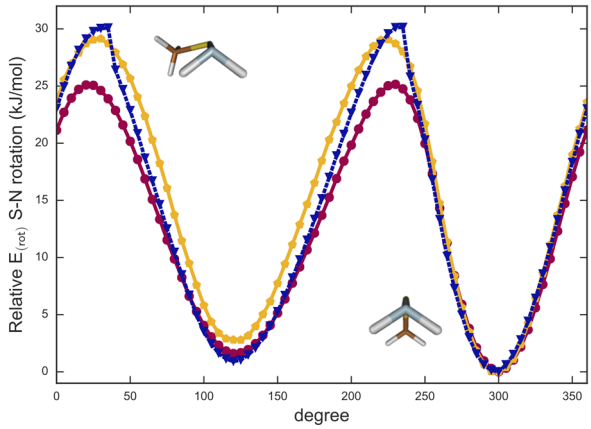


Figure 2: 360◦ rotation of R-groups; tertbutane (-⬟-), methane (-●-), and benzene (-▼-) about the sulfur-nitrogen bond, for the sulfenamide species. Representative geometry for methanesulfenamide at respective maximum and minimum. For all other species please see **SI Figure 7**.

Table 2: Calculated S-N bond length during rotation about S-N bond, at local minimum and maximum, in Å.

	1a	1b	1c	2a	2b	2c	3a	3b	3c
S-N min	1.74	1.74	1.70	1.74	1.73	1.71	1.73	1.73	1.69
S-N max	1.81	1.78	1.72	1.81	1.78	1.73	1.79	1.79	1.72

Conclusions

Sulfonamides and its reduced congeners have historically been particularly difficult moieties to study due to a lack of methods for direct measurement. By applying S K-edge XAS to directly investigate how the sulfur atom interacts with its nearest neighbors we can gain an insight into the nature of the sulfur-nitrogen bond of sulfinated amides. Our studies point to minimal π-contributions in the sulfur-nitrogen bond.

Experimental

Materials

Methanesulfonamide (98% purity) and benzenesulfonamide (≥98% purity) were purchased from Sigma-Aldrich. Methanesulfonamide: ^{1}H NMR (300 MHz, DMSO) δ 2.91 (s, 3H, CH_3), δ 6.80 (s, 2H, NH_2); Benzenesulfonamide: ^{1}H NMR (300 MHz, DMSO) δ 7.83 (d, 2H, J=6Hz), δ 7.58 (m, 3H), δ 7.35 (s, 2H). Tertbutanesulfinamide (Ellman's sulfinamide) were synthesized in the laboratory of Scott Bohle at McGill University.

XAS Acquisition and Data Analysis

Sulfur K-edge XAS data for 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 200-500mA. 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 ($Na_2S_2C_3$) with the first pre-edge feature being calibrated at 2472.02 eV (21).

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 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_o), calibrated and averaged with the Blueprint- XAS (22) prefit function. Only the first scans of tertbutanesulfinamide were used due to sulfur photoreduction in the fluorescence data. As TEY does not exhibit such photoreduction, 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 (23). The number of components for fits were estimated by employing the Akaike information criterion (AIC) (24) (25). 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 paper.

Self-absorption corrections were not applied to the XAS data obtained for **2b**, **3a**, and **3c**; for this reason, detailed intensity analyses of the data were not performed.

DFT

All gas phase DFT calculations were run using ORCA, version 2.9.0 (26), using spin-unrestricted Kohn-Sham equations with 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 (19).

SUPPORTING INFORMATION

The following files are available free of charge: simulated TD-DFT spectra, LUMO diagrams, maximum and minimum rotational energy plots and geometries, Mulliken Population Analysis and Kohn-Sham Orbital tables.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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ABBREVIATIONS

XAS, X-ray Absorption Spectroscopy; TD-DFT, Time Dependent - Density Functional Theory

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